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RESECTION OF ANGINAL PATHWAY FOR RELIEF OF ANGINAL PAIN*

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WE first became interested in the possibility of relieving anginal pain in patients undergoing splanchnicectomy who had severe hypertension and angina pectoris. After the pioneer work of White,[1] who discovered the correct anatomic pathway in the wake of earlier, less accurate French exploration, it was only a step to extend the high dorsolumbar sympathectomy upward to include the first to the fourth thoracic ganglion.

It is true that we and other neurosurgeons had noted relief of anginal pain in many hypertensive patients who had had sympathectomies too low to include the anginal pathway.[2-4] Our experience in this regard is shown in Table 1.

TABLE 1. *Relief of Anginal Pain in Hypertensive Patients According to Level of Resection.**

SERIES	NO. OF PATIENTS	EXTENT OF RESECTION	PATIENTS OBTAINING SATISFACTORY RELIEF %
I	0	12th thoracic to 2d or 3d lumbar segment	(Angina avoided)
II	8	Between 12th thoracic and 5th to 3rd lumbar segment	12.5
III	15	4th thoracic to 3d lumbar segment	73.0
IV	10	Various parts of anginal pathway	100.0

*Based on Evans et al.[5]

White and Bland,[6] Grimson et al.[7] and Kinsey and Smithwick[8] had already performed high sympathectomies, including all or part of the pathway, on patients with hypertension and angina.

OBSERVATIONS ON THE ANGINAL PATHWAY

The anginal pathway is composed of sympathetic fibers passing through the inferior cervical fused with the first thoracic ganglion (stellate ganglion), and direct fibers from the cardiac plexus passing through the first, second, third and fourth thoracic ganglions (Fig. 1). Resection of the cervical ganglions only, as first performed by Jonnesco,[9] proved a failure because of these direct fibers. According to White and Bland,[6] the afferent pain fibers, stimulated by cardiac anoxia and running in the middle and inferior cardiac nerves, pass downward through the inferior cervical ganglion, which is usually fused with the first thoracic ganglion to form the stellate ganglion. From there these fibers pass through the white ramus connecting the first thoracic ganglion to the spinal cord. There are also direct connections from the cardiac plexus that pass through the first, second and third, and probably the fourth, thoracic ganglions.

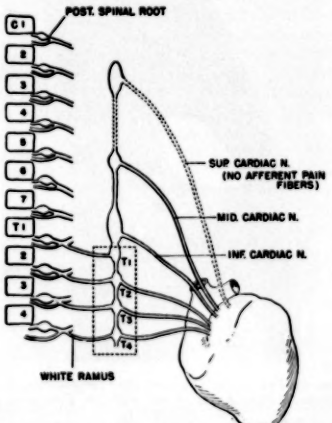

FIGURE 1. *The Cardiac Afferent Pain Pathway (Reproduced from Evans et al.[5] with the Permission of the Publishers). Note how the anginal pathway is funneled through the first, second, third and fourth thoracic ganglions.*

Although White[1] is not certain that pain fibers from the heart pass through the fourth thoracic ganglion, we are inclined to believe that they often do, because extension of the resection level from a

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point below the fourth thoracic ganglion to include this ganglion in splanchnicectomies for hypertension with angina pectoris increased relief of anginal pain in from 12.5 to 73 per cent of cases. This notable increase in satisfactory results cannot be due solely to relief of the cardiac load from drop in blood pressure or to prolonged rest after operation. White and Bland[6] reported a case in which it was necessary to resect the fourth thoracic sympathetic ganglion on the left before a good result was obtained. One of our patients with angina, from whom only the second and third thoracic ganglions were removed bilaterally for Raynaud's disease and scleroderma, continued to have attacks of pain in the left arm. Removal of the fourth thoracic ganglion in this case was not necessary to abolish the substernal pain component, which disappeared after the operation. It seems that the persistent pain in the left arm in this patient was mediated through the first left thoracic ganglion. This case is not included in the reported series because the patient did not have hypertension and the operation was not purposely designed to relieve the angina, the fear being entertained at that date of robbing her of warning anginal pain. Two similar cases are included in the series; in these, pain in the left arm persisted when the first thoracic ganglion on the left was not resected. However, pain in the left arm disappeared in 3 patients whose first thoracic ganglions were untouched. We have often noted other inconsistencies of sympathetic pathways. For instance, resection of the first three lumbar sympathetic ganglions bilaterally does not invariably paralyze ejaculation; resection of the fourth thoracic ganglion — sometimes only on one side — stops axillary sweating in most patients but not in all.

FIGURE 2. *The Upper End of the Sympathetic Resection (Reproduced from Evans et al.[5] with the Permission of the Publishers).*

Careful analysis of our first series[5] of 10 hypertensive patients revealed that complete relief of anginal pain was obtained in 5 cases, the first thoracic ganglion on the left being resected in 4. In 2 of these patients, not even throat pain occurred after operation. The weight of evidence, therefore, seems to favor the importance of including the first thoracic ganglion in the resection to increase the chance of obtaining complete relief. Since pain recurred on the right in 2 patients who did not have resection of the right anginal pathway, we now advise bilateral resection to the level of the first thoracic sympathetic ganglion. This decision is consistent with the well recognized anatomic facts demonstrated by White and Bland[6] and, previously, in animal experiments by White, Garrey and Atkins.[1]

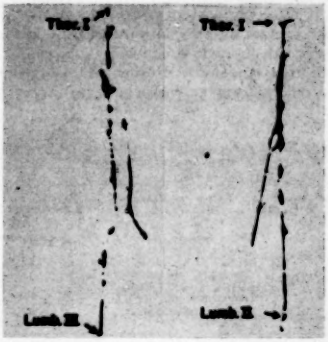

FIGURE 3. *Specimens Removed in Sympathectomy from the Stellate Ganglion to the Third Lumbar Ganglion in Cases of Hypertension with Severe Angina (Reproduced from Evans et al.[5] with the Permission of the Publishers).*

As we embarked gradually on these procedures, our hesitancy to carry resection immediately up to the stellate ganglion was caused by the desire to avoid ptosis. In some cases it is difficult to avoid resection of the upper part of the stellate ganglion and the production of a Horner syndrome if fusion of the first thoracic with the inferior cervical ganglion is too close. None of our patients in whom ptosis occurred complained, however, and it has

been our observation that, in time, the ptosis becomes less decided. Table 1 shows that the higher the resection, the better the results, especially on the left side.

It is of interest that when anginal pain is still provoked after operations to the level of the fourth thoracic ganglion, the pattern of pain is never altered, whereas resection of any part of the anginal pathway invariably alters the pattern, except in Case 14, in which the operation was a complete failure. If any pain does persist, it is usually in the throat or jaw, especially if resection of the first to the fourth thoracic ganglion is performed.

Technic of Operation

The operative technic used for the removal of the stellate ganglion and the thoracic sympathetic chain in the hypertensive patient is identical to that previously described by Poppen[10] for extensive combined thoracolumbar sympathectomy, except that the incision is extended approximately 4 cm. cephalad. The medial portion of the fifth rib is removed as well as the eighth and eleventh ribs instead of the seventh and eleventh ribs as previously described. Thus, excellent extrapleural exposure of the upper thoracic sympathetic chain and ganglions (Fig. 2) is achieved. The entire thoracic sympathetic system, including the stellate ganglion, may be removed in this manner (Fig. 3). In the normotensive patient only the fourth rib is partially resected.

General Results

Encouraged by our results in the relief of anginal pain in hypertensive patients, we resected the anginal pathway (the first to the fourth thoracic ganglion) in 2 patients without hypertension. We believe that this operation should be offered to the normotensive patient with angina only if he has an "over-alarm" syndrome — that is, if the provocation of pain is out of proportion to the need for protection of the heart. These patients have angina of emotion and often angina decubitus. Although they may have a well healed coronary infarction, they are regarded as reasonably safe from another immediate coronary occlusion and thus as a safe operative risk. In 1 case we waited nine months to prove to our satisfaction that the patient was not going to have an early recurrent infarction.

Of the 14 cases of hypertension reported, there was severe disabling angina in 13. Since angina had been relieved in 73 per cent of 15 patients who had resection from below to above the level of the fourth thoracic ganglion, we believe that the hypertensive patient with a mild anginal syndrome does not need the higher resection, with its added technical difficulties.

It is not to be expected that all patients will obtain complete relief of all distress. In fact, one argument advanced against the operation is robbing the patient of a danger signal designed by nature to limit his activities and thus to prevent cardiac strain. Therefore, our designation of "satisfactory" simply means, at the minimum, that the patient has been sufficiently relieved to become an active citizen, capable of most activities. (This also means an extremely grateful patient in every case marked "satisfactory.")

High thoracolumbar sympathectomy (Table 2) was performed in a series of 14 hypertensive patients, all except 1 of whom had severe disabling angina pectoris. Among the 14, only 1 had had probable coronary infarction (Case 8), but all presumably had coronary insufficiency. The operation was also done on 2 patients who had angina without hypertension; both had angina decubitus, 1 presumably with syphilitic stenosis of the coronary ostia with typical nocturnal dyspnea and anginal pain. The follow-up period for the total series of 16 patients was six months to three years. Complete atrioventricular dissociation developed postoperatively in 1 patient, presumably as a result of painless coronary occlusion (Case 13). At six months he was free of chest pain. Complete relief, except for a residual sensation of constriction in the throat, was obtained in 9, or more than half the cases. Partial but satisfactory relief of pain occurred in 4 patients, 1 of whom (Case 5) had been bedridden because of status anginosus; merely turning in bed caused pain. Although she still suffers mild substernal pain, which causes her to stop and rest, she is active, does all her housework and goes on shopping trips. One patient (Case 1), who was partially relieved for three years, died at the end of that interval of a coronary infarction, at which time she suffered substernal pain. In another (Case 12), with a result rated as "poor," angina was completely relieved for seven months, when she presumably suffered a coronary infarction with pain in the jaw only; this patient reverted to the same limited exercise tolerance experienced before operation owing to pain in the jaw, which was relieved by nitroglycerin. Case 16, one of the 2 normotensive patients, was also relieved for three months except for jaw pain, when he, too, suffered a coronary infarction, which brought back the original pain. One patient (Case 14) of the 16 must be considered a complete failure. He had hypertension (Grade 1) with angina of effort and emotion and had a complete thoracic sympathectomy from the first to the twelfth thoracic ganglion. The pain was not modified in distribution or exercise tolerance. It did not recur on emotion. He still sweats in the axillas. One may speculate that sympathetic fibers may still be present in the posterior roots in this case.

Discussion

All our hypertensive patients undergoing extensive sympathectomy had fairly severe symptoms

TABLE 2. *Results of Sympathectomy.*

Case No.	Age	Sex	Preoperative Status	Level of Sympathectomy		Follow-up Period	Present Status	Result
				Left	Right			
	yr.							
Patients with hypertension:								
1	42	F	Grade 3 hypertension; angina pectoris; Dupuytren's contracture.	3d thoracic to 2d lumbar	6th thoracic to 2d lumbar	3 yr.	Pain, chiefly right sided, before operation; pain continued, but less severe after operation; patient died 9/11/49 of coronary occlusion.	Satisfactory for 3 yr.; partial relief.
2	46	F	Grade 2 hypertension; angina pectoris.	Inferior stellate to 2d lumbar	3d thoracic to 3d lumbar	3 yr.	No angina	Satisfactory; complete relief.
3	47	F	Grade 2 hypertension; angina pectoris.	3d thoracic to 2d lumbar	Through stellate to 2d lumbar	2 yr., 8 mo.	Slight angina; negative exercise-tolerance test; occasional pain in throat and left arm on exertion.	Satisfactory; partial relief.
4	41	M	Grade 3 hypertension; angina pectoris; substernal pressure on exertion after meals.	2d thoracic to 2d lumbar	2d thoracic to 2d lumbar	2 yr., 9 mo.	No pain	Satisfactory; complete relief.
5	49	F	Grade 3 hypertension; angina pectoris; diabetes mellitus.	Below stellate to 2d lumbar	4th thoracic to 2d lumbar	2 yr.	Considering bedridden existence, relief dramatic but only partial	Satisfactory; partial relief.
6	42	M	Grade 3 hypertension; angina pectoris (old posterior coronary infarction observed on electrocardiogram).	7th thoracic to 1st lumbar (1943); below stellate through 9th thoracic (1948).	7th thoracic to 2d lumbar (1943); through stellate to 7th thoracic (1948).	20 mo.	1943-1948, angina continued; positive exercise-tolerance test; 1948, no pain; hot sensation in throat and arm; infarct (Sept., 1949) but normal electrocardiogram.	Satisfactory; partial relief.
7	49	F	Grade 2 hypertension; angina pectoris; right-bundle-branch block.	2d thoracic to 2d lumbar	4th thoracic to 2d lumbar	3 yr.	Right-bundle-branch block; no pain or throat symptoms; dyspnea only.	Satisfactory; complete relief.
8	54	F	Grade 3 hypertension; intractable angina pectoris.	Inferior stellate to 2d lumbar	Inferior stellate to 2d lumbar	1 yr., 4 mo.	No angina; pain in throat on exertion.	Satisfactory; complete relief, except for throat.
9	45	M	Grade 2 hypertension; angina pectoris; Dupuytren's contracture.	Below stellate to 3d lumbar	3d thoracic to 2d lumbar	1 yr.	No pain, but constriction in throat on exertion; Dupuytren's contracture better on left, worse on right.	Satisfactory; complete relief, except for throat.
10	44	F	Grade 3 hypertension; strain and failure of left ventricle (nocturnal dyspnea); angina pectoris; cardiac enlargement; aortic atherosclerosis.	1st thoracic to 2d lumbar	4th thoracic to 2d lumbar	2 yr.	No pain; no nocturnal dyspnea; transverse diameter, 0.7 cm. less; "strain" pattern disappeared.	Satisfactory; complete relief.
11	47	F	Grade 2 hypertension; effort angina on walking half block.	1st to 12th thoracic	1st to 12th thoracic	18 mo.	No anginal pain; electrocardiogram normal.	Satisfactory; complete relief.
12	54	F	Grade 2 hypertension; diabetes mellitus; angina 4 yr., day and night; 10 nitroglycerin pills daily; diphasic T wave in Lead CF4.	1st to 12th thoracic	1st to 12th thoracic	1 yr.	Complete relief for 7 mo., followed by probable coronary infarction; jaw pain relieved by nitroglycerin; exercise-tolerance test same as before operation; electrocardiogram showed septal infarction.	Poor; partial relief.
13	44	M	Grade 3 hypertension; mild effort angina on inclines; mild cerebrovascular accident.	2d to 12th thoracic	1st thoracic to 1st lumbar	18 mo.	Complete atrioventricular dissociation after operation; constriction of throat on talking or facing cold.	Satisfactory; complete relief, except for throat.
14	34	M	Grade 1 hypertension; angina of effort and emotion; positive exercise-tolerance test.	1st to 12th thoracic	1st to 12th thoracic	7 mo.	Same chest pain at same exercise level; no pain with emotion; exercise-tolerance test with electrocardiogram still positive; question of aberrant, nonresected pathway.	Failure
Patients without hypertension:								
15	38	F	Syphilitic stenosis of coronary ostia; nocturnal angina with smothering 5 to 10 times per night; severe angina on effort.	1st to 4th thoracic	1st to 4th thoracic	9 mo.	Persistence of nocturnal smothering; no effort or nocturnal angina.	Satisfactory; complete relief, except for throat.
16	40	M	Arteriosclerotic heart disease, with angina pectoris	1st to 4th thoracic	1st to 4th thoracic	6 mo.	Pain in jaw and constriction of throat with emotion when tired — rarely with unusual effort; no chest pain; return of pain after coronary infarction 4 mo. after operation.	Poor

of postural hypotension for about six months after operation, but only the most severely ill patient, who had status anginosus (Case 5), experienced angina on sudden standing. Resection in this case was limited to below the stellate to the second lumbar ganglion on the left and to the fourth thoracic to the second lumbar ganglion on the right. The postural hypotension after extensive thoracolumbar sympathectomy might be expected to lower the head of pressure in the coronary system and decrease coronary irrigation, thereby producing angina on standing. We found this to be true only in this case, in which the angina was not severe. The reason that extended exercise tolerance occurs may be that coronary dilatation actually takes place after sympathectomy, rather than constriction as was formerly taught. This idea is strengthened by the fact that patients who were left with a residual warning throat pain had this pain at a greatly increased exercise-tolerance level.

Excessive anginal pain far out of proportion to any necessity of protecting the heart from overexertion, such as angina decubitus and the angina of emotion, may occur by the same mechanism as in reflex sympathetic dystrophy or causalgia of a limb. Certainly, the psychic background of these patients is similar. The theory of the internuncial pool of Lorente de Nó[11] may explain the unwarranted amount of pain of some patients with angina. This consideration has led us to extend the operation into the field of severe emotional angina, angina decubitus and status anginosus in normotensive patients without too much coronary damage or too recent a coronary infarction.

That the mechanism of reflex sympathetic dystrophy may pertain is further borne out by the improvement of a Dupuytren's contracture in the left hand of 1 patient (Case 9), in whom resection was carried out to the first thoracic ganglion on the left, whereas Dupuytren's contracture in the right hand became worse when resection was done only to the level of the third thoracic sympathetic ganglion. Kehl[12] reported 6 cases of Dupuytren's contracture that followed coronary-artery disease and infarction. Therefore, good results might be expected from sympathectomy in cases of the shoulder-hand syndrome, a rare complication of coronary-artery disease described by Hilker.[13] The hand changes reported by Johnson[14] in 21.8 per cent of patients with myocardial infarction suggest a reflex sympathetic dystrophy induced by cardiac pain. These observations enhance the rationale of sympathectomy for anginal pain.

Case 8 illustrates increased work capacity before throat constriction occurs. This patient had hypertension (Grade 3) and probably remote anterolateral myocardial infarction. For eighteen months before sympathectomy she had been incapacitated and unable to do any housework or to walk in cold weather. Sixteen months after resection of the first thoracic to the second lumbar sympathetic ganglion on the left and the third thoracic to the second lumbar ganglion on the right she reported a new sensation of pain in the throat, extending to both lower jaws. This pain was so unfamiliar to her and so different from her old anginal pain that she attributed it to a small, nontoxic colloid adenomatous goiter and thought its removal might help. Only on careful questioning did it become apparent that this pain also occurred on effort but only after much greater exertion than that required to cause pain before operation. In fact she did all her housework and went shopping in any weather. Her blood pressure was still 230 systolic, 110 diastolic, as compared with 250 systolic, 124 diastolic, before operation. At that time, almost a year and a half after operation, no intervening coronary attacks had occurred, so the extended exercise tolerance could not be attributed to reduction of cardiac load, prolonged rest after operation or the relief of effort angina that sometimes comes after a coronary infarction.

To illustrate further the possibility of increased coronary flow after sympathectomy, the electrocardiographic exercise-tolerance test in Case 3 changed from positive to negative. This patient still has occasional pain in the throat and left arm on exertion two years and eight months after resection of the third thoracic to the second lumbar ganglion on the left and the first thoracic to the second lumbar ganglion on the right.

The disappearance of the throat constriction and all pain in 2 patients is probably the result of extension of exercise tolerance incident to increased coronary flow since it is unknown whether the pain pathway mediating a sense of throat constriction is resected — where these fibers travel is also not known.

In Case 1, a patient who died three years after operation, relief was partial, though satisfactory. In this early patient resection extended only to the sixth thoracic ganglion on the right, and thus did not include any of the anginal pathway on that side, although the pain, preoperatively, was mainly on the right side. Sweating could be demonstrated over the right side of the chest and the right arm after operation, which proved that the most important pathway in this case was not touched at all. Our experience with this patient bears out White's[1] contention that cardiac pain is mediated to the right by the right cardiac nerves and to the left by the left cardiac nerves.

In Case 6 resection to the seventh thoracic ganglion was performed in 1943 without relief of the severe angina. When reoperation, with resection to the second thoracic ganglion on the left and the first thoracic ganglion on the right, was performed for angina and persistent hypertension, gratifying relief was obtained.

Minor disadvantages of the operation including the anginal pathway are the ptosis of Horner's

syndrome, postural hypotension, severe sweating in the groins and swollen nasal membranes (noted by Grimson et al.[7]) Swollen nasal membranes occurred in 2 of our patients, but tended to subside early.

Conclusions

Resection of various parts of the sympathetic anginal pathway (the first to the fourth thoracic ganglion on the right and left) achieved a satisfactory result in 13 of 16 patients. Relief of anginal pain was complete in 5, complete except for a residual sense of throat constriction in 4 and satisfactory in 4.

Best results were obtained in patients who had complete resection of the anginal pathway (the first to the fourth thoracic ganglion) bilaterally.

Throat or jaw pain was not a constant residual finding. It is possible that the relief of even this unblocked pain results from the decreased strain on the heart of the hypertensive patient as well as increased exercise tolerance, or by actual dilatation of the coronary bed.

The relief of status anginosus suggests that its mechanism is actually that of reflex sympathetic dystrophy.

The possible production of a Horner syndrome is not considered a contraindication to the operation of resection of the anginal pathway in view of the relief obtained from previous disability.

The operation should be confined to patients with severe angina associated with hypertension, and to normotensive patients who have an "over-alarm" syndrome and who have not had a recent coronary infarction.

Since this paper was submitted for publication 2 additional patients with "over-alarm" syndromes have been operated on. The psychic overlay in these patients was great. The results were not satisfactory: in 1 patient pain in the back took the place of the old chest pain, and the second has retained the same pattern. In general, we believe that the results will always be more satisfactory in the hypertensive patient with angina.

References

1. White, J. C., Garrey, W. E., and Atkins, J. A. Cardiac innervation: experimental and clinical studies. *Arch. Surg.* 26:765-786, 1933.
2. Peet, M. M. Hypertension and its surgical treatment by bilateral supradiaphragmatic splanchnicectomy. *Am. J. Surg.* 75:48-68, 1948.
3. *Idem.* Results of bilateral supradiaphragmatic splanchnicectomy for arterial hypertension. *New Eng. J. Med.* 236:270-277, 1947.
4. Isberg, E. M., and Peet, M. M. Influence of supradiaphragmatic splanchnicectomy on heart in hypertension. *Am. Heart J.* 35: 567-583, 1948.
5. Evans, J. A., Poppen, J. L., and Tobias, J. B. Relief of angina pectoris by sympathectomy: report of results in 10 patients subjected to high thoracolumbar sympathectomy including anginal pathway. *J. A. M. A.* 144:1432-1436, 1950.
6. White, J. C., and Bland, E. F. Surgical relief of severe angina pectoris: methods employed and end results in 83 patients. *Medicine* 27:1-42, 1948.
7. Grimson, K. S., Orgain, E. S., Anderson, B., Broome, R. A., Jr., and Longino, F. H. Results of treatment of patients with hypertension by total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy. *Ann. Surg.* 129: 850-871, 1949.
8. Kinsey, D., and Smithwick, R. H. Early experiences with total thoracic sympathectomy in hypertensive patients with coronary heart disease and angina pectoris. *Proc. New Eng. Heart A.*, 1946-1947. P. 63.
9. Jonnesco, T. Operative cure of angina pectoris. *Bull. Acad. de méd., Paris* 84:93-102, 1920
10. Poppen, J. L. Extensive combined thoracolumbar sympathectomy in hypertension. *Surg., Gynec. & Obst.* 86:1117-1123, 1947.
11. Lorente de Nó, R. Analysis of activity of chains of internuncial neurons. *J. Neurophysiol.* 1:207-244, 1938.
12. Kehl, K. C. Dupuytren's contracture as sequel to coronary artery disease and myocardial infarction. *Ann. Int. Med.* 19:213-233, 1943.
13. Hilker, A. W. Shoulder-hand syndrome: complication of coronary artery disease. *Ann. Int. Med.* 31:303-311, 1949.
14. Johnson, A. C. Disabling changes in hands resembling sclerodactylia following myocardial infarction. *Ann. Int. Med.* 19:433-456, 1943.

FEVER AS A SIGN OF QUINIDINE TOXICITY

Report of Sensitivity in Two Brothers with Thyroid Disease

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TOXIC reactions to quinidine are often dermal or gastrointestinal except when large doses cause myocardial disturbances, such as intraventricular block, ventricular tachycardia and ventricular fibrillation.

In 1952 Berley and Saland[1] called attention to the relatively uncommon occurrence of drug fever from quinidine, and stated that 5 cases had been reported. In 3 of these there were also skin reactions. The authors presented 2 more cases in which fever was the only evidence of toxicity.

Rose, Vogl and Turtz,[2] in 1953, reviewed the literature and added 3 cases of their own. These, the 2 described by Levy[3] and the 2 cases reported below bring the total to 14 in which the febrile response was predominant.

Each of us treated with quinidine 1 of 2 brothers with auricular fibrillation and thyroid hyperfunction. This is the only record of familial sensitivity to quinidine with drug fever of which we are aware.

Case 1. A 42-year-old man was first seen on March 1, 1949, because of bronchitis. The blood pressure was 160/102, and he had frequent premature beats. He smoked 60 cigarettes a day. On April 1, 1951, he was re-examined for the Coast Guard. He was flushed and sweaty. His blood pressure was 132/82. An electrocardiogram showed auricular fibrillation of the coarse type.

The basal metabolic rate was +22 per cent. X-ray examination of the heart was negative. The course of therapy is shown in Figure 1. He received quinidine sulfate by mouth for 11 days in daily doses of 1.6-3.0 gm. (24-45 gr.), without toxic reaction or effect on the arrhythmia except the conversion to auricular flutter. It was then omitted for 2 days and resumed at 2 gm. (30 gr.) for 1 day. Fever appeared on that day (April 24), and

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the temperature reached 105°F. the next day. The drug was omitted, and heparin and digitalis administered, the apical rate falling to 80. Propylthiouracil, 150 mg. a day, had been started on April 18, and on April 28 the basal metabolic rate was +5 per cent, and the serum cholesterol 151 mg. per 100 cc.

After omission for 4 days quinidine was resumed in a total amount of 0.8 gm. (12 gr.) in 2 doses. A temperature of 105°F. immediately returned, with accompanying diarrhea. One other trial of the drug was attempted on May 16, with a similar reaction after a dose of 0.2 gm. (3 gr.). Pronestyl, 0.25 gm. every 4 hours, was then given. Three days later the dose was increased to 0.5 gm. at the same intervals; there was no effect on the arrhythmia.

Since that time therapy has been directed toward control of the hyperthyroidism with propylthiouracil and lipo-iodine. In November, 1951, the thyroid gland became diffusely enlarged for the first time, and it appeared more obvious that the problem

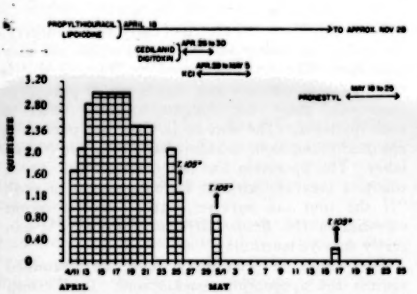

FIGURE 1. *Dosage of Quinidine, with Three Febrile Responses, in Case 1.*

Note the delay in the appearance of fever on the first occasion, but the immediate reaction when quinidine was resumed on April 24, May 1 and May 16. Other medications are shown.

was one of incompletely controlled hyperthyroidism. The patient continues to feel well, but marked sweating and auricular fibrillation persist.

CASE 2. E. F., the 48-year-old brother of E. F., was first seen on January 21, 1952. One month before, the patient had discovered a mass in the right side of the neck associated with some deepening of his voice that had been present for two months. Upon admission to the hospital, with a diagnosis of cystic thyroid disease, he was found to have auricular fibrillation with a ventricular rate of 110. He had no cardiac symptoms, was not nervous and had gained some weight. The basal metabolic rate was +22 per cent. Hemithyroidectomy on the right was performed on January 22. Microscopical examination confirmed the cystic disease but also showed hyperfunctioning thyroid tissue. The postoperative basal metabolic rate was −3 per cent.

The patient was given 3 doses of quinidine sulfate, 0.4 gm. at 2-hour intervals, and normal rhythm was restored. He was placed on a maintenance dose of 0.2 gm. 4 times a day and discharged from the hospital on January 28. A week later, he had four loose stools, and, in the evening nausea, vomiting and a shaking chill. The temperature was 104°F. by mouth. Quinidine was omitted the next day. The temperature remained at 102°F. for 2 days, but recovery was complete by the 4th day except that irregular heart action had returned.

Auricular fibrillation of the coarse flutter type was demonstrated by electrocardiogram on February 11. The patient was readmitted to the hospital 6 days later and on the following day was given 0.2 gm. of quinidine at 3, 6 and 8 p.m. Chilliness, diarrhea and headache continued, and it was decided to change to Pronestyl, 0.25 gm. four times a day by mouth. Auricular fibrillation, however, recurred in the afternoon of February 19, and on February 20, 0.5 gm. of Pronestyl was given at 8 a.m., 12 noon and 4 p.m. Normal rhythm reappeared, and he was discharged on a dose of 0.5 gm. 4 times a day. He stopped smoking and gained 8 pounds in weight and so began to smoke again. Between June and October auricular fibrillation recurred in spite of a daily dose of 2 gm. of Pronestyl. He was not aware of the arrhythmia, but an electrocardiogram revealed coarse fibrillation with a ventricular rate of 100 and ectopic beats.

On October 28, Gitaligin (amorphous gitalin) therapy, 0.5 mg. 3 times a day for 4 days, was begun, with a maintenance dose of 0.5 mg. daily thereafter. Normal rhythm, except for ventricular premature beats, appeared by November 1, and on this dose of Gitaligin it has persisted. He has reduced his weight by 14 pounds, still smokes 20 cigarettes a day and feels well.

DISCUSSION

The unusual features in the medical history of these 2 brothers are the occurrence of identical febrile reactions to quinidine, the cryptic type of hyperthyroidism and the relatively slow ventricular rate associated with the coarse type of auricular fibrillation even during the periods when digitalis was not being given.

Rose, Vogl and Turtz[2] have commented on the criteria for the diagnosis of fever due to quinidine. Our cases confirm their observations on sensitization by previous doses, discrepancy between the height of the fever and the well-being of the patient, and the rapid defervescence of the fever twenty-four to forty-eight hours after the drug has been omitted.

Auricular fibrillation, the arrhythmia for which quinidine is most frequently administered, should be considered, in New England at least, to be associated with rheumatic mitral stenosis until disproved. Failing this diagnosis, hyperthyroidism should be diligently searched for by determination of the basal metabolic rate and serum cholesterol, and often by the added tests of radioactive iodine uptake and protein-bound iodine. In older persons degenerative heart disease is often associated with auricular fibrillation. Finally, this arrhythmia may be present as a benign or "idiopathic" condition, often occurring in paroxysms over many years.

The greatest complication of auricular fibrillation is embolism. Berley and Saland[1] point out that a sudden rise in temperature suggests embolism or bacterial endocarditis. When such a rise occurs in a patient receiving quinidine, the drug should be stopped before these other diagnoses are seriously suspected, in the absence of other overt signs of arterial obstruction or blood-stream infection.

Certainly, any use of antibiotics in the presence of drug fever is to be deplored since this will only complicate the situation.

SUMMARY

Two brothers with mild thyrotoxicosis and auricular fibrillation are described. Both had drug fever (temperature of 104 to 105°F.) that was due to quinidine. The only other toxic reaction was mild diarrhea.

Auricular fibrillation persists in 1 case treated with propylthiouracil, Pronestyl and digitalis medication. The arrhythmia in the other brother, treated

by surgical removal of cystic thyroid tissue, has been restored to normal on three separate occasions with each of these drugs.

Quinidine sensitivity in the form of drug fever is rare but should not be mistaken for cardiovascular or other complications in patients receiving this medication.

References

1. Berley, B. S., and Saland, G. Febrile hypersensitivity to quinidine given orally. *J. A. M. A.* 148:1121, 1952.
2. Rose, O. A., Vogt, A., and Turtz, A. I. Drug fever due to quinidine. *New Eng. J. Med.* 248:96-98, 1953.
3. Levy, R. L. Clinical toxicology of quinidine. *J. A. M. A.* 79:1108-1113, 1922.

ETHICS OF PSYCHOSURGERY*

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SURGICAL operations on the brain for the treatment of functional mental disorder continue to disturb the conscience of many thoughtful and sympathetic persons, physicians and others. It is timely and proper, therefore, that the ethics of psychosurgery should be discussed. Enough factual material is available for a fairly precise postoperative picture of the patient to be presented and compared with the ideal of human attainment. This was not so in the beginning of psychosurgery. Indeed, Burckhardt presented the moral problem as long ago as 1890. His words seem to have a particular relevance to the present discussion:

> Doctors are different by nature. One stands fast on the old principle: *primum non nocere:* the other states: *melius anceps remedium quam nullum.* . . . I belong naturally to the second category. Every new surgical approach must find its special indications and contraindications and methods, and every path that leads to new victories is lined with the crosses of the dead. I do not believe that we should allow this to hold us back from approaching the goal, the healing of our patients by surgical methods. The purely medical side of our calling must and shall lead us, *nolens volens*, along this pathway.

Time is necessary for the germination of ideas. Burckhardt's work was forgotten in the enthusiasm for the newly developing neurologic surgery. When the symposium on the frontal lobe was presented at the Second International Congress in 1935, Egas Moniz was probably the only one who saw in the data supplied what he needed for filling out the theory on which he based prefrontal leukotomy. In fact, as Fulton[1] tells the story, Moniz asked whether operations on man could be undertaken that would have similar effects to those that Fulton and Jacobsen have performed on trained chimpanzees, making them immune to frustration. Another important event was Brickner's report at the same meeting of a man whose frontal lobes had been removed by Dandy to extirpate a large meningioma. Brickner[2] stated that his patient was "the same sort of person," in spite of obvious defects in initiative and self-restraint.

From this historical sketch of early psychosurgery, two principal basing points arise to which one may hold fast. The first, expressed by Burckhardt,[3] is that men are different and that some, in pursuit of their aim, must face dangers to bring relief to their patients. The second is that the patient is essentially the same person after losing his frontal lobes. The operation has not changed him into a robot, a creature without feeling, without a soul. "If the soul can survive death," says a recent editorial in the *British Medical Journal*,[4] "it can surely survive leucotomy."

The ethics of leukotomy must be examined against the appropriate background. In Western civilization the concept of innate dignity, the inherent quality of the individual, has grown and flowered. To feed and clothe the poor, comfort the unfortunate and try to heal the sick are regarded as duties of society, as is kindness to animals and to children. One applauds the courageous loser, the underdog, and views with horror the atavistic trends of totalitarian states, the mass experiments even more than the victims of gas chambers and machine guns, who at least died quickly and without suffering. The infliction of needless suffering is utterly condemned.

On the other hand Americans have not learned to live with one another to the extent that they can eliminate or even greatly reduce the psychologic suffering in their environment. They are an aggressive people, and their aggressions and hostilities, curbed in their physical expression, are apt to find outlet in disagreeable psychologic attitudes and subtle violence that leave no mark upon them or their victims, but yet lead to certain types of expression — neurotic, psychotic, criminal, alcoholic and so on — that betray the inner tensions. Here one is dealing with a background that is far from homogeneous, an *ethos* that protects the weak from the dominant, and an aggressive spirit that finds its best outlet in constructive assaults upon nature, organized contests of sports and relentless search for the good of humanity. Among these different people are some who will heed the Hippocratic axiom, "*primum non nocere*," and others who are

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led, *nolens, volens*, along the road to "the healing of our patients by surgical methods."

A certain tolerance and encouragement might well be accorded those who think differently and try to do things in new ways, even if their first gropings in the dark meet with failure and frustration. These researchers are presumably honest and will turn back if they see that their results are falling short of reasonable expectations.

The second part of the background concerns the patients. There are several characteristics of candidates for leukotomy that deserve consideration. For one thing, they are suffering. This distress is so great that the patients are faced with disability or suicide. Many of them are destructive and violent. Presumably they are driven to desperation by their inner experiences; otherwise, they would not behave in such fashion. Whether these experiences consist in bitter hostility or terrible self-loathing or anguished response to vivid hallucinations, the effect upon the patients is catastrophic. Confinement is essential for their own welfare as well as for the safety of others. Isolation and sometimes restraint may be required to prevent ghastly consequences.

Candidates for leukotomy have passed beyond help from milder methods. In this state of emotional turmoil, they are inaccessible to personal influence; the various shock methods relieve those whose cases are less severe and thus make operation unnecessary. Patients are selected for leukotomy from the residue when other methods fail.

Another characteristic of candidates for psychosurgery is their tendency to progress downward into greater degrees of disability and deterioration. No surgeon or psychiatrist would be inclined to undertake leukotomy unless reasonably certain that this was a method of last resort, necessary to break through the vicious circle of anxiety, obsessive thinking and depression that defies the efforts of the well meaning physician to bring the patient back to health.

Leukotomy is applied characteristically, but not exclusively to patients who, on a statistical basis, may be considered hopeless from the standpoint of rehabilitation. The time factor is the most important of all thus far studied. It is assumed that once a patient has entered a mental hospital, he is already in a chronic stage of his disease. Treatment outside the hospital (I am speaking of civil hospitals) has failed. Statistics show that chronicity is a serious bar to resumption of productive existence. Two out of 3 patients subjected to operation during the first six months of their hospitalization can return to work or keep house or attend school. After a year of hospitalization, about half the patients can be rehabilitated, whereas after two years, only 1 out of 3 can return to productive existence. The percentage of social recoveries after leukotomy falls thereafter, but some patients can be returned to their homes after ten or even twenty or more years of hospitalization. The percentage is low.

What happens to patients in mental hospitals who have passed the two-year period? What are their chances, without operation, of returning home and of again participating in a natural social existence, earning a living, managing a house and so on. Again, statistically, their chances rapidly reach the vanishing point, being approximately 5 per cent according to Malzberg.[4] Of course, there is the famous story, repeated in every hospital, of the patient who had been in a catatonic stupor for ten years when the doctor held up the sunken chin and told him of his mother's death. "Is that so?" said the patient — and was home in a week. (This form of therapy may be all right, but it is a little hard on Mom.)

Some years ago I made a study of longevity at St. Elizabeth's Hospital. Plotted on logarithmic paper, there was a precipitate drop in the first year, most of the senile and arteriosclerotic patients surviving but a short time. Then the curve flattened out, with a gradual decline until the base was reached at about the seventieth year. For a number of years John Washington was the "oldest inhabitant" of St. Elizabeth's Hospital, having been admitted in 1881 as a youth of nineteen. When I last saw him, he was ninety years old. In visits to other mental hospitals, I have been introduced to similar patients, old men and women, whose life was blighted at an early age and who spent the rest of their existence behind locked doors.

It is too late to help these old people. They have stopped fighting. They have surrendered to their preoccupations and live permanently in their world of fantasy. But the question arises whether it is not possible to help some of their juniors who are still fighting, who have not retreated to their infantile omnipotence. Of these younger men and women confined for two years in a mental hospital, only 5 in 100 will recover sufficiently to leave the hospital; 10 will survive for forty to fifty years. The rest will die between two and forty years after admission.

This, then, is the background of clinical material that must be considered in a discussion of the ethics of leukotomy. Sooner or later one will have to ask whether these patients should be denied the chance of restoration to effective living through surgery.

Before an answer is made, however, it is imperative to examine the effect of leukotomy upon the patient. If it is true that the operation destroys the personality, rendering the patient a soulless robot, the conscience of the psychosurgeon must indeed be a hardy one if he undertakes even a handful of such mutilating operations. Opinions differ most vehemently on this aspect of the problem.

There are two main reasons why this should be so.

The first pertains to the type of patient most frequently examined after leukotomy — namely, the patient with chronic schizophrenia. This might be called the "broken-mainspring" type. Hoffman compares these patients to a broken watch; after it is shaken it ticks for a few seconds as though nothing were wrong, but then it runs down and stops. Deteriorated or desocialized schizophrenic patients are particularly noticeable in their behavior when, after leukotomy, they are again able to sit at a table and push a floor mop instead of being confined in a "quiet" room. The devastating effects of the psychosis upon the personality are all too evident. Another type is what Ackerly calls the faded angel. Here the drive for misbehavior has been curbed, but aside from a pleasant exterior, there is little inner tension that greets the examiner when he probes the deeper ranges of the individual. This result of operation frequently reflects the completeness of the separation of the frontal lobes from the rest of the brain. Too limited operation upon the frontal lobes is useless, and too extensive operation is ruinous. When a nonpsychotic patient has undergone a radical lobotomy, he exhibits all the boy-scout virtues in reverse. Such patients are fortunately becoming more rare as the partial and selective operations on the frontal lobe are becoming more widely adopted. To assess properly the results of leukotomy on the personality, nondeteriorated patients must be chosen, and the operation must have been performed as conservatively as possible.

When these requirements are met, one deals with a person who is to all intents and purposes normal. He has recovered from a harassing and disabling illness and is endowed with sufficient energy, imagination, judgment and foresight to handle his problems as well as he could before the illness. Some patients reach an even higher degree of social effectiveness than they had attained before their illness. Even creativeness can be observed in certain patients.

When stabilization has occurred (this process may require two years after prefrontal lobotomy or one year after transorbital leukotomy or bimedial leukotomy or topectomy) the losses of the personality are minimal and are completely offset by certain gains in social effectiveness. Thus, whereas the patient shows a measurable loss in self-criticism, he is not paralyzed by feelings of inadequacy; he may be hasty in making up his mind, but he is no longer tormented by doubt; and although he is somewhat indolent, he is no longer making himself and everybody else uncomfortable by a ceaseless urge to perfection. It is true that in comparison with his status before illness, he is lacking in self-criticism, in deliberation and in creative zeal. This, essentially, is the price that he must pay to be relieved of a disabling functional neurosis or psychosis. The other personality defects, large and small, can be explained by the loss of such qualities either during the psychosis or as the result of a needlessly extensive operation. From the practical standpoint, the surgeon should err on the conservative side in performing any operation on the frontal lobe. It is better to reoperate than to make the incisions too extensive.

What of the ethics of leukotomy in a patient tormented by doubts, fears and continual harassment from fancied inadequacies, persecutions, anguish, remorse and intractable pain? Are physicians justified in surgical attack upon the brain for the relief of such symptoms, meanwhile knowing that something of the patient's personality must be sacrificed in the process? The answer will lie with the orientation of the physician, his philosophy, his reaction to the suffering of the patient and his knowledge of the natural history of the affliction from which the patient is suffering. Granting that leukotomy is a gross method, akin to Alexander's cutting of the Gordian knot that he did not have the patience to unravel, granting that the operation is a palliative measure, designed to reduce the symptoms of anxiety and preoccupation with the self, granting even that accidents may occur, with resulting disability and death, there is this to be said about leukotomy: that it is an effective means of returning a third of apparently incurable patients to their homes and of relieving distress in half the remainder. This is the positive side of the medal. The negative side — the personality losses that can properly be attributed to leukotomy — is considered to comprise less than 10 per cent of the patients subjected to operation.

It is the function of the surgeon so to operate that the hazards of leukotomy will be still further reduced and that the social complications as well as the physical complications will be reduced to a minimum. It is the function of the co-operating psychiatrist to select patients who will benefit most from operation and to bring them to operation before the deteriorating and desocializing effects of the mental disorder have ruined their chances of effective community life. And it is the function of the physician, in whatever field of work he may be engaged, to press forward in search for new and better methods of treating the patients who now occupy more than half the hospital beds in this country.

Some argue that a psychosis or a neurosis is a fiery furnace in which the dross is burned away and the basic personality remains behind as a molten mass of pure gold. But is it? Can one put this down as another rationalization, another compensation on the part of the psychiatrist for his failure to heal the patient? The noble calling is devoted to healing the sick and relieving suffering. Relieving pain looms large in other branches of medicine, and mental pain or anguish is often more real than physical pain. It is equally fictitious and mislead-

ing to deny to the suffering patient a vigorous attempt at relief by taking refuge in the argument that the psychotic or neurotic behavior represents an expression of the personality of the patient and that it would be unwise if not immoral to interfere with the workings of nature. This specious argument, another example of shielding devices employed by the ineffective therapist to justify his persistence in futile remedies, savors of the arguments advanced a century ago concerning the relief of pain in general surgery, only even more without foundation. Suffering of the spirit, the breakdown of the mind, brings in its train a weakened psychic structure. Relapses or subsequent attacks are rendered more likely. The patient is sensitized to the harmful influences within and without and falls more easily a prey to later disturbances, with increased tendency to fixation. Mental disorders play havoc with morale, and although leukotomy cannot always restore morale to its pristine condition, at least it can abolish the overwhelming load of anguish that accompanies demoralization.

A few words about morale. Morale is the inner quality that makes the group more important than the individual. When a man sickens psychologically, the focus of his attention changes from the group of which he is a member toward himself. This exaltation of the ego at the expense of the group is an evil influence on the group as a whole — whether it is the family, squad or business organization. The repercussions of a mentally sick person on the group must be considered one of the by-products of mental disorder. If the demoralized person, thinking only of himself, cannot be restored and again play an effective role in his organization, he must be removed from the group to prevent spreading demoralization and disaster to the whole. Fortunately, the performance of leukotomy before the group has disintegrated and when there is still a place in the group for the member after his disorder is relieved will rebuild the group into a harmonious and effective whole. I have in my files literally hundreds of letters attesting this restorative effect of the operation upon the family group. As one husband said, "Doctor, you should have operated on her thirty years ago."

Leukotomy seems to be morally and ethically justified when certain conditions can be met. The patient must be suffering severely, sufficiently so that he is faced with disability or suicide. He must be afflicted with a malady that, as far as one can tell, is not going to respond favorably to any less drastic means of therapy. Finally, the good effects of operation in the relief of suffering and restoration to effective living must not be overbalanced by losses in the socially desirable qualities *that the patient still retains*. It is essential when one is assessing the probable results of operation to take the patient as he is in the here and now rather than as he used to be or might have been if the mental disorder had not interrupted his career. Ethically and morally, some surgeons feel justified in attempting by leukotomy to bring to the suffering of the patient a certain peace of mind upon which they can then build as much of a superstructure as possible of social graces and effective community expression, morale.

References

1. Fulton, J. F. *Frontal Lobotomy and Affective Behavior: A neurophysiological analysis.* 159 pp. New York: Norton, 1951.
2. Brickner, R. M. *The Intellectual Functions of the Frontal Lobes: A study based upon observation of a man after partial bilateral frontal lobectomy.* 354 pp. New York: Macmillan, 1936.
3. Burckhardt, G. Über Rindenexcisionen, als Beitrag zur operativen Therapie der Psychosen. *Allg. Ztschr. f. Psychiat.* 47:463-548, 1890-91.
4. Editorial. Ethics of leucotomy. *Brit. M. J.* 1:909, 1952.
5. Malzberg, B. Rates of discharge and rates of mortality among first admissions to New York civil state hospitals. *Ment. Hyg.* 36: 104-120 and 618-638, 1952.

SPONTANEOUS EXTRAVASATION FROM THE URETER SECONDARY TO ANEURYSM OF THE ABDOMINAL AORTA*

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RECENTLY the 27th case of spontaneous or nontraumatic extravasation from the ureter was reported. The purpose of the present communication is to present a case secondary to an arteriosclerotic aneurysm of the abdominal aorta. In Orkin's[1] comprehensive paper, the 26 cases previously recorded in the world literature were summarized.

The effect of such an aneurysm on the upper urinary tract has been described. Linton[2] states that the retroperitoneal structures most frequently affected are the ureters. Mistaken urologic diagnoses have included perinephric abscess, renal colic, hydronephrosis, renal tumor and perirenal hemorrhage. Actual urologic disturbances secondary to the aneurysms include hydronephrosis, perirenal hematoma, perinephric abscess, renal colic, hematuria, anuria, uremia and obliteration of the psoas-muscle margins,[3] as well as spontaneous rupture of the ureter, as in the case reported below. The illustrations recently presented by Wilkinson[4] clearly show the relation of the aneurysm of the abdominal aorta to the ureters, and help explain the complications secondary to the impingement of the aneurysm on the ureters.

CASE REPORT

A 63-year-old diesel operator was admitted to the hospital in September, 1951, because of recurrent bilateral inguinal hernias. Systemic review revealed urinary hesitancy and nocturia. Physical examination showed Grade 1 hypertensive changes of the ocular fundi. The blood pressure was 170/110. The heart was not enlarged. There were bilateral recurrent inguinal hernias. The prostate was moderately enlarged. Significant laboratory data included a nonprotein nitrogen of 37 mg. per 100 cc. and a phenolsulfonephthalein excretion of 70 per cent in 2 hours. X-ray examination of the chest revealed considerable tortuosity of the aorta.

The bladder neck and prostate were resected. Postoperatively the patient was asymptomatic, and he was discharged on the 7th postoperative day.

Follow-up examination revealed that he had no further urinary complaints. However, he complained of backache and pain in the left buttock radiating down the left leg. Orthopedic and neurologic investigation failed to disclose a specific cause for these complaints.

The patient was readmitted to the hospital in January, 1952, for herniorrhaphy. Abdominal examination revealed a smooth, slightly tender, pulsating mass in the midportion of the abdomen, just to the right of the midline. A gastrointestinal x-ray examination showed enlargement of the duodenal loop. Excretory urograms demonstrated no abnormality of the kidneys, but both ureters were displaced toward the right. It was thought that an aneurysm of the abdominal aorta was displacing the right ureter laterally and that adhesions about the aneurysm were drawing the left ureter to the right. The aneurysm was believed to be of recent origin, but it was decided to observe the patient at frequent intervals to determine if the mass became larger and symptomatic before an operation on the aneurysm was attempted.

On January 22 the left inguinal hernia was repaired, and a left orchiectomy was performed to effect a better closure of the internal ring. The postoperative course was uneventful, and the patient was discharged on the 9th postoperative day.

Six months later, in June, 1952, he complained of pain in the right flank radiating anteriorly. Examination showed mild costovertebral-angle tenderness on the right. The aneurysm apparently had not changed in size. The urinary sediment contained occasional red and white cells.

During the next 4 weeks he complained of increasing right subcostal and flank pain, pain in both thighs and numbness of the legs. Admission was advised for further study.

He was readmitted to the hospital in July, when there was tenderness in both flanks, more marked on the right. The previously described pulsating mass was again palpated in the right midportion of the abdomen. The blood pressure was 190/100 in the arms and 210/100 in the legs. Significant laboratory data consisted of a hematocrit of 32 per cent, nonprotein nitrogen of 68 mg. per 100 cc. and 7 to 10 red cells and 3 or 4 white cells per high-power field in the sediment. Cultures were positive for *Aerobacter aerogenes*, *Pseudomonas aeruginosa* and *Proteus vulgaris*.

Within 2 days the patient's condition changed considerably. The pain in the back increased, and he became nauseated and began to vomit. Fullness and marked tenderness developed in the right flank. At this time the nonprotein nitrogen rose to 89 mg. per 100 cc.; the hemoglobin was 10.5 gm. per 100 cc., and because it was thought that the aneurysm had begun to bleed a transfusion was given.

Throughout the 2d day the patient did not void. He was catheterized, and only 35 cc. of urine was obtained; the catheter was left indwelling. Vomiting, however, was excessive. For the next 2 days the patient was maintained on intravenous infusions of fluids, the urinary output increasing to normal amounts so that the catheter was removed. He continued to improve during the next 3 days and was able to take fluids by mouth.

During the period of vomiting, and when the nonprotein nitrogen was elevated, an intravenous pyelogram was done, but was unsatisfactory. Examination on the 8th hospital day revealed constant dribbling of urine and a soft, cystic, suprapubic mass extending to within 2 fingerbreadths of the umbilicus. There was exquisite tenderness in the right loin and flank, with a sensation of fullness in the right flank. There was slight left-costovertebral-angle tenderness, but no fullness on that side. Rectal examination revealed an enlarged prostate. The suprapubic mass could be felt on bimanual examination.

On the basis of this examination, the suprapubic mass was regarded as representing a full bladder, and the fullness in the right flank as an enlarged kidney or retroperitoneal tumor, such as a hematoma. Immediate bladder catheterization was performed, 1500 cc. of urine being obtained; the suprapubic mass disappeared. The catheter was left indwelling.

The patient's condition remained essentially unchanged during the next few days. On the 12th hospital day, cystoscopy and retrograde pyelography were done without anesthesia. The ureters were catheterized easily with No. 5F ureteral catheters. Aspiration revealed 61 cc. of urine from the right pelvis and 40 cc. from the left. Retrograde injection of Skiodan revealed bilateral hydronephrosis and minimal hydroureter in the upper halves of the ureters, a marked change since the previous January. The most interesting finding was the extravasation of opaque medium from the right ureter during the retrograde

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injection (Fig. 1). The point of extravasation was approximately 6 cm. below the pelvis. Both ureters were displaced, suggesting a retroperitoneal mass eroding the right ureter.

It was believed that the aneurysm had displaced both ureters and, by pressure on them, had caused hydronephrosis. Extravasation from the right ureter was probably due to necrosis of the ureter and not to the passage of the catheter, for there had been no pain during its passage and none on injection of the Skiodan.

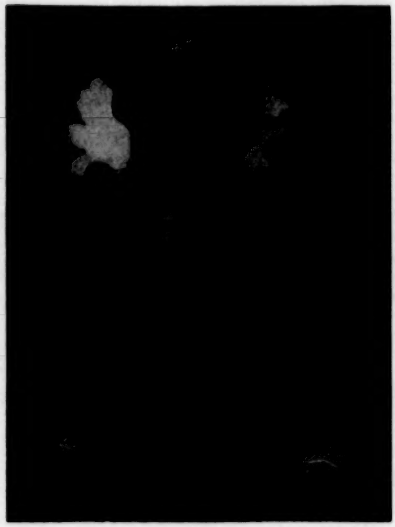

FIGURE 1. *Film Taken Ten Minutes after Removal of the Ureteral Catheters.*

Note almost complete retention of the medium in both kidneys and the upper third of the ureters, as well as the extravasation on the right.

On the afternoon before exploration No. 6F ureteral catheters were easily passed and left in place.

On August 1, under general endotracheal anesthesia operation was performed. The aneurysm extended down to the bifurcation of the aorta and up to just below the inferior margin of the pancreas. The right ureter passed under the saccular dilatation and could not be followed into the kidney. The left ureter was pushed laterally and also could not be followed into the kidney. Considerable reaction was noted between the wall of the aneurysm and the retroperitoneal structures. Through an aneurysm needle, approximately 200 feet of buffed No. 30 steel wire was packed into the aorta according to the "pack" method described by Linton.[3] The patient tolerated the procedure well.

The ureteral catheters were left in place and drained well. On the 2d postoperative day the temperature began to spike to 103°F., with chills and sweating. Urine flow and output remained good, and Gantrisin was given intravenously as a urinary antiseptic.

On the following day, with the ureteral catheters still in place, retrograde injection was repeated before the catheters were removed. The films revealed the presence of the wire packed tightly in the abdominal aorta overlying the 3rd, 4th and 5th lumbar vertebras. The bilateral gross hydronephrosis was again noted (Fig. 2).

On the 8th day after operation the urethral catheter was removed but had to be replaced on the next day when the patient again had difficulty in voiding. The nonprotein nitrogen during this time ranged from 49 to 59 mg. per 100 cc.

On the night of the 13th postoperative day, the patient complained of abdominal pain, and examination revealed a dehiscence of the upper portion of the wound. The wound was repaired immediately, and thereafter his improvement was progressive. On the 19th day the catheter was again removed, and repeated determinations of residual urine declined progressively from 450 cc. to 150 cc.

A repeat intravenous pyelogram on September 2 showed the bilateral hydronephrosis with poor function on the right. The patient was discharged 5 weeks after the wiring of the aneurysm, when the nonprotein nitrogen was 38 mg. per 100 cc.

He was followed at periodic intervals and readmitted on October 21 for re-evaluation. Examination revealed a large incisional hernia in the midportion of the abdomen. Through the defect the wired aortic aneurysm could be felt. The hematocrit was 28 per cent; pyuria was now present, culture growing *P. mirabilis*. The nonprotein nitrogen was 45 mg. per 100 cc.; the phenolsulfonephthalein excretion was 25 per cent in 2 hours.

FIGURE 2. *Film Taken Three Days after Wiring of the Aneurysm Showing the Wire in Situ and Skin-Retention Sutures Overlying the Right Side of the Abdomen.*

Hydronephrosis and dilatation of the upper ureter are still present.

X-ray study of the chest showed an aneurysmal dilatation in the descending thoracic portion of the aorta, and excretory urography bilateral hydronephrosis, with less concentration of the dye on the right side. There was no evidence of extravasation of urine from the ureter.

Determinations of residual urine demonstrated a progressive decrease in amount, and patient was able to pass a maximum of 450 cc. at a time. It was decided that it was not necessary to resect the bladder neck and prostate, and he was discharged.

Follow-up examination in January, 1953, revealed a residual urine of 55 cc. The only complaints were persistence of back pain. The patient was able to return to his former occupation in a part-time capacity.

Discussion

Orkin,[1] in his comprehensive review, stated that "spontaneous rupture of the ureter is invariably secondary to pyelo- or ureterolithiasis, since a calculus could either be demonstrated or recovered in 23 of these cases." In the case reported above, calculi were not found, and the radiographic, cystoscopic and surgical evidence pointed to the aneurysm as the cause of the extrinsic obstruction bilaterally and of the extravasation from the right upper ureter.

This patient was not subjected to drainage of the retroperitoneal space because there was no indication that he had any additional pain at the time of extravasation of the Skiodan during retrograde pyelography. The extravasation probably occurred before the cystoscopy since the patient had a pain of sudden onset in the right loin and flank, followed by a tender fullness in the right flank, *three weeks before the cystoscopy*. The ureteral catheter passed to the kidney pelvis and was not seen outside the ureter at any time, nor was there any obstruction to the passage of the catheter or any sudden pain or other symptom, as from ureteral perforation (the retrograde studies were done without anesthesia). Radiographic and surgical findings demonstrated that both upper ureters were firmly adherent to the aneurysm, and that the ureteral obstruction was undoubtedly secondary to the aneurysmal dilatation.

Summary and Conclusions

A case of aneurysm of the abdominal aorta with bilateral hydronephrosis and spontaneous rupture of the ureter is reported. Although the effect of such an aneurysm on the upper urinary tracts has often been described, this is believed to be the first case to be reported with rupture of the ureter secondary to the aneurysm.

Wiring of the aneurysm effected a pronounced improvement in the patient's urologic status.

In all cases of hydronephrosis of extrarenal origin, aneurysm of the abdominal aorta should be considered as a possible cause.

References

1. Orkin, L. A. Spontaneous or nontraumatic extravasation from ureter. *J. Urol.* 67:272-283, 1952.
2. Linton, R. R. Intrasaccular wiring of abdominal arteriosclerotic aortic aneurysms by "pack" method. *Angiology* 2:485-497, 1951.
3. Uhle, C. A. W. Significance of aneurysm of abdominal aorta masquerading as primary urologic disease: case reported. *J. Urol.* 45:13-40, 1941.
4. Wilkinson, W. R. Abdominal aortic aneurysm: report of case treated with reactive cellophane. *Surg., Gynec. & Obst.* 96:82-86, 1953.

Additional References

Bahnson, H. T. Definitive treatment of saccular aneurysms of aorta with excision of sac and aortic suture. *Surg., Gynec. & Obst.* 96:383-402, 1953.

De Takats, G., and Marshall, M. R. Surgical treatment of arteriosclerotic aneurysms of abdominal aorta. *Arch. Surg.* 64:307-319, 1952.

MEDICAL PROGRESS

FOOD POISONING (Continued)

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SAN FRANCISCO

Salmonella Gastroenteritis

Salmonella gastroenteritis is apparently more carefully diagnosed than some of the other types of food poisoning. Feig[9] found 72 outbreaks (3430 cases); 40 were termed "food poisoning," and 32, "gastroenteritis." They represent 14.6 per cent of the total of 476 outbreaks reported for a three-year period. In 1951 only 15 outbreaks (850 clinical cases) were reported. Although the specific salmonella involved was not determined in 30 (42 per cent) of the 72 outbreaks, at least there is evidence that the organism was demonstrated in either the stools or the food or both and in only 2 cases was merely suspected as the causative agent. Four of the 30 inadequately typed strains were at least classed according to the Kauffmann–White scheme as Group C.

Within a period of ten years great changes have taken place in this group. The unreliability of former statistics applicable to salmonella food infections was brought about through the ascription to salmonella of many outbreaks in which viable organisms were not found, or through inherent difficulties of isolating the organism actually present in the spoiled food or in the feces of the patients. Since 1945 improved enrichment-culture technics and vastly greater experience have certainly furnished more dependable records. The statistics from England and Wales[10, 11] are particularly informative. During 1949, 2431 sporadic cases, large outbreaks and family outbreaks were reported; of these, 1369 (56 per cent) were attributed to salmonella. In 1950, 51 per cent of the total incidents were caused by salmonella. Salmonella gastroenteritis seems to be at least four times more prevalent in Great Britain than in North America. At first sight these findings place the salmonella group in the

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position that it held in the United States until the early 1930's, when staphylococci were recognized as causes of food poisoning. But this conclusion must be modified when it is appreciated that 90 per cent of the so-called outbreaks affected individuals and that only 10 per cent affected groups. Staphylococci, on the other hand, affected only groups, no sporadic cases being listed in the statistics for the United States. The main reason for this difference between salmonella and staphylococcal infections is the great difficulty in detecting sporadic cases of staphylococcal gastroenteritis or poisoning from other organisms. Knowledge of these forms of poisoning is restricted to outbreaks in which large numbers of persons are usually affected.

British epidemiologists reason that the incidence of the different bacterial types of food poisoning is probably reflected better in outbreaks in the ordinary sense of the term than in the narrower sense of any infection, whether of a single person or of a group simultaneously infected from the same apparent source. On this basis, 40 per cent of the outbreaks are caused by salmonella, 20 per cent by staphylococci, and 40 per cent by other organisms. Sporadic cases of salmonella infections are apparently more common in England and Wales, or, much more probably, thanks to an excellent public-health laboratory service, they are being recognized more frequently. An apparent shift in incidence took place in the Hawaiian Islands, when an exceedingly competent bacteriologist, interested in enteric-fever organisms, reorganized the laboratory services. Because of the proportion of the figures, however, it seems likely that outbreaks of salmonella gastroenteritis are about three times as frequent in England and Wales as they are in the United States. A search for comparative statistics covering other European countries during recent years has not been very successful, but salmonellas have always been considered the commonest cause of food poisoning in Germany, Belgium and France. The only report, from the East Zone of Germany,[49] mentions for the year 1948 a total of 2045 cases of meat poisoning. Fifty-six cases, with 12 deaths, were investigated, and in 35 the responsible food was bacteriologically examined. Only 9 yielded salmonella, and the remainder contained proteus and coliform organisms.

Why do the two continents differ in the incidence of salmonella outbreaks? The usual comment that European epidemiologists and health officers are unfamiliar with staphylococcal gastroenteritis may have been justified before 1945, but an increasing number of critical examinations of single outbreaks by experts since that time invalidates it. There is no evidence that European investigators continue to focus their attention solely on salmonellas. In fact, this comment might now be made about American epidemiologists and their attention to staphylococcal outbreaks. Here, under the impact of the studies by Dack, Dolman and others, the "ptomaine" hypothesis, which was a fitting explanation of many common explosive outbreaks of food poisoning, was rejuvenated by the realization that not protein decomposition products but autolyzed staphylococci disturb the gastrointestinal tract. Until the novelty of this discovery has reversed the swing of the pendulum, overestimation of staphylococcal gastroenteritis is understandable. One must search further for the answer and give consideration to two other factors.

The first is that the cause of nearly 50 per cent of the reported outbreaks in the United States is undetermined. Several thoughtful epidemiologists have expressed the belief that many of these may be due to salmonellas. They call attention to the fact that the salmonella reservoirs in animals and man are about equal on both continents. This is true. The detailed studies on salmonella infections by Seligmann, Saphra and Wassermann,[50] by Seligmann and Saphra,[51] by Edwards, Bruner and Moran,[52] by Felsenfeld and Young,[53] and by Bynoe, Bailey and Laidley[54] in the United States and Canada and the records of the Public Health Laboratory Service of the British Ministry of Health[10, 11, 55, 56] support the statement. Secondly, since the common denominator in salmonellosis is the contamination of food by feces or by any other means that results in the ingestion of salmonella and since water serves as a vehicle for these bacteria only rarely, it is reasonable to consider most of the outbreaks food borne. For over sixty years the literature on salmonellosis dealt with food-borne outbreaks. In fact, it was considered synonymous with food poisoning. The knowledge that contact with pets and other animals not used for food and with sick persons or healthy carriers may be links in this infection chain led to a new interpretation of the term salmonellosis. There are reasons to suspect that during this transition the official records dealing primarily with food poisoning have been deprived of group infections due to salmonella, now being included with salmonellosis. The higher incidence in Great Britain may not be as striking as the incomplete records for the United States indicate.

The probability that the difference is real provokes an afterthought, perhaps relevant to other food-borne diseases as well. Food habits, particularly the handling and preserving of foods, may contribute their share to the difference. It would be profitable to know how food hygiene in Europe differs from that in the United States. In a series of articles on food poisoning as a national problem, Conybeare[57] compared the high standards of care and cleanliness in preparing and distributing food in the United States with the admittedly low standards in Great Britain, where meat inspection, for example, leaves a great deal to be desired. It appeared to him futile to draft regulations to pre-

vent infection when corned beef, too often eaten without reheating several days after the initial cooking, is wrapped in the butcher shop with raw carcass meat. Emergency slaughtering of fatally infected animals is still practiced in Europe. This was, incidentally, responsible for the first proved salmonella food poisoning in Germany[58, 59] and for the episode in Moorseele, Belgium,[60, 61] which proved that the meat product may appear sound and yet carry the seed of death. In the Belgian episode the meat inspector who had approved the carcass was so convinced of the purity of the meat that he volunteered to prove his point by eating some of the sausage. He did not survive the experiment. Federal and state meat inspection in the United States, though considered wasteful in many ways, has undoubtedly prevented many salmonella infections. Furthermore, the increasing consciousness and demands of the public and the catering services to raise standards in the preparation and distribution of food may be responsible for the apparent lower incidence of proved salmonella gastroenteritis in the United States.

The practitioners who see the victims of a food-poisoning episode and pass the information to the investigative agency in the health department must realize that the constant use of the laboratory is essential to prove a true etiologic association between a suspected food and the illness of the patient. A variety of mediums are efficient in revealing certain strains of salmonellas in fecal or food specimens. Culture on tetrathionate enrichment broth with subculture on sodium desoxycholate citrate agar is superior to any other procedure.[62] Some laboratories do first-class "research"; others, overworked with other tasks, are either indifferent or fail to appreciate that the salmonella diagnostic centers (Communicable Disease Center, Atlanta, Georgia and several other public-health service laboratories) throughout the country gladly co-operate in typing the cultures. Precise diagnosis, which is urgently needed to provide the necessary guide to prevention, has an immediate practical bearing on public-health procedures.

Clinical Manifestations

This is a true bacterial infection. The salmonellas multiply in the gastrointestinal tract and produce symptoms after incubation of usually 12 to 24 hours, occasionally more or less. The mean, calculated from an analysis of 54 outbreaks or cases, varied from 17.9 to 18.2 hours. The onset may be abrupt, with chills, headache, cramping, abdominal pains, vomiting and diarrhea. The temperature almost always rises. Nausea and vomiting are not prominent, and in fact may not occur. Since the clinical patterns of the gastroenteritides may be quite similar, the difference in incubation period is generally considered an important differential feature. The duration and severity of the disease vary in different outbreaks and from one person to the next. The patient may be better within a week, but it may be a fortnight before he is strong again. The stools are foul smelling and soon become watery. Accurate diagnosis depends on recovering the same pathogenic salmonella from the stools and the ingested food. Fatal infections in the young and the aged have been reported. Published mortality rates up to 1920 varied from 0.2 to 1.5 per cent[63]; an average of 2.8 per cent was given for a recent three-year period in the United States.[1]

Treatment

Treatment is the same as that recommended for staphylococcal gastroenteritis. Most salmonella infections fail to respond to sulfonamide therapy. Chloramphenicol has been tried to clear carriers, but in the doses used there was no significant statistical difference in the results between the 25 treated and the 25 untreated patients.[64]

Epidemiology

The core of this problem is closely interwoven with the serologic classification of the causative bacteria, inaugurated by Bruce White[65] and Kauffmann.[66] The establishment of centers all over the world has been an important step not only toward recognizing but also toward identifying and tracing the salmonella serotypes in their reservoirs and peregrinations. Over 256 serotypes have now been distinguished.[67] Only 14 different types have been isolated from outbreaks of food poisoning. If the data of Seligmann, Saphra and Wassermann[68] are taken with the provisions previously indicated, at least 44 different types have played their roles in the United States, though not necessarily in association with food poisoning outbreaks. In the Belgian Congo at least 46 serotypes are known as potential agents of food infections; 39 were isolated from man, and 14 from animals.[68] Before World War II, 14 different types had been isolated from episodes in England and Wales, but after the retail distribution of spray-dried eggs, imported from the United States, in 1942 a large number of "exogenous" types were recognized. By 1949 another 47 types had been added to the already known salmonellas there. In the year 1950 alone, of the 49 identified types, 16 belonged to those common in England and Wales, described as "endogenous," whereas 33 were identified after 1940 and are described as "exogenous." The ratio of exogenous to endogenous types was 1:15 in 1950, 1:20 in 1949. Since about 10 per cent of the samples of dried eggs tested were found to be contaminated with salmonella, since the new types found in cases of food poisoning belonged to the same types and occurred in the same order of frequency as those in dried eggs and since the chronologic correspondence between the importation of dried eggs and the cultivation of the new serotypes from patients with food poisoning was

very close, the conclusion is drawn that the new types were imported and spread by dried eggs.[69] More recent observations — for example, in Germany[70] — have supported the correctness of this conclusion: salmonella gastroenteritis occurred in a prisoner-of-war hospital in 1947 after the prisoners ate scrambled eggs prepared from an American dried-egg powder. Bacteriologic examination of the original egg powder showed no salmonellas, but the stools of the severely infected contained *Salmonella tennessee*, a type principally, if not solely, found in fowl.[69] In Great Britain the decrease in the proportion of exogenous types coincided with the decrease in the amount of dried eggs imported. No satisfactory explanation has been offered for the interesting fact that only 2 reported outbreaks of human salmonellosis have been traced to eggs in the shell.[71, 72] In Great Britain examination of 3648 hen's eggs from various sources at home and abroad yielded no members of the salmonella group.[73]

All over the world, one type — *Salmonella typhimurium* (the old *Bacterium aertrycke*) — is most common; it is isolated in the United States and Canada in 30 to 40 per cent of all outbreaks of salmonella gastroenteritis and in Great Britain in two thirds of all outbreaks of salmonella gastroenteritis. The interchange of this type between animals and man can now be traced more definitely through the use of Vi-phage typing. All the recent reports from England specifically record the phage types. In the United States the next most common, in descending order of frequency, are *S. newport, oranienburg, cholerae suis, anatum, montevideo* and *panama*. The statistics for England and Wales list a different sequence: *thompson, enteritidis, newport* and *montevideo*. Other types — *derby, give, manhattan, newington, miarin, berta, javiana, dublin* — are often met with, and still other types of insufficient importance for mention here are isolated occasionally.

S. enteritidis, which has an important position in the lists of England and Wales and to some extent in Canada, is represented in only 3 American outbreaks between 1945 and 1951; only 1.4 per cent of the salmonellas cultured from man were of this type. This organism is a parasite of fowl, appears frequently in rodents and has been used in Great Britain as a rat poison with the intent of instituting fatal rat epizootics. The results are not satisfactory, and sometimes the infection is conveyed to man. Whether this practice accounts for the higher incidence of this type cannot be judged from the available histories. The danger was recognized long ago in this country, and many states prohibit the sale of salmonella cultures as rat poison. Most of the *S. enteritidis* infections have been traced to duck eggs.

The infrequency of isolation of *S. thompson* from poultry and swine is reflected in the rarity of human infections due to this type in the United States. In England it has been found in the majority of outbreaks among ducks in recent years,[74] but no infections in human patients have arisen from this source. Pets may carry this type, though no cases in human beings have been contracted from them.

S. dublin, a common parasite of the intestinal tract of apparently healthy cattle, appears rarely in the outbreaks in the United States. Thirty-one outbreaks studied in England and Wales in 1946 and 1947, and 24 in 1949 were attributed to this type. In a recent study in northern Ireland the incidence was 8.6 per cent in healthy cattle.[75] During culture of samples of feces from excreters of *S. thompson*, other types — *gallinarum, enteritidis, typhimurium, kentucky* and *oregon* — were discovered.

An increased incidence of infections due to *S. panama* and to others of the paratyphoid C group was reported from the northern Rhine-Westphalia region in 1950 and 1951.[76] Most infections were severe, and 6 deaths among 233 cases of single and group infections were attributed to *S. panama*, apparently originating from contamination of various foods by excreters.

Pathogenicity and Pathogenesis

Ever since salmonellas were first isolated, efforts have been made to discover their pathogenicity. Individual human beings react differently to the ingestion of the well recognized types. The apparent infrequency of salmonella gastroenteritis in man, in spite of the widespread infection in domestic animals and their products used for food suggested measurement of the pathogenicity on small laboratory animals. When inoculated, many salmonellas proved quite pathogenic for rodents, and on peroral administration the virulence for rats differed markedly.[77, 78] Living cultures of *Salmonella typhimurium* and *enteritidis* caused watery diarrhea and general malaise with loss of appetite in *Macaca mulatta* monkeys.[79] Eleven different serotypes isolated from the intestines of chickens produced symptoms or signs of illness when 50 cc. of veal infusion-broth cultures was fed to primates.[80] When animal experiments led to no conclusions, feeding the organisms to human volunteers (which with one exception had been delayed for fifty years) became necessary. The only previous human experiment, feeding 5 volunteers with from 2,000,000,000 to 4,000,000,000 *S. typhimurium* isolated in a fatal case of a six-month-old child, was undertaken to support the assumption that large doses are required to infect man.[81] These adults tolerated ingestion without suffering any symptoms at all, or only mild afebrile diarrhea. However, in clinical experience infants and old persons appear to be considerably more susceptible, and fatal cases are restricted to these two age groups.[80]

The unusually high incidence (26 per cent) of deaths in infections due to *S. cholerae suis* attests

to a specific strain characteristic of enhanced virulence, but this characteristic cannot be measured by feeding experiments on primates. The fatal infections with other types, except *S. typhimurium* (6.2 per cent) and *oranienburg* (6.1 per cent), are too few for individual statistical evaluation. With the steady increase in the number of types isolated from eggs and egg products, it became important to know whether these types are pathogenic for man. On the basis of expert epidemiologic inquiries, the pathogenicity of some of these species was unquestionable, but for others it was not known. In fact, until McCullough[82] and McCullough and Eisele[83, 84] studied a series of cases of carefully planned and executed experimental salmonellosis in human beings, the pathogenicity of certain strains isolated from spray-dried whole-egg powder was not fully known. By feeding three strains each of *S. meleagridis* and *anatum* and one each of *newport*, *derby* and *barrilly* in graduated doses, these authors determined the minimal infective dose for man. All were pathogenic, but infectivity varied a great deal. One strain of *S. meleagridis* produced illness at levels of 7,000,000 to 10,000,000, whereas 44,500,000 to 67,200,000 of *S. anatum* were required to cause disease, varying from mild brief enteritis to serious prostrating illness. With both *S. barrilly* and *newport* the small dose of 125,000 and 152,000, respectively, resulted in illness; in fact, the illness was severe enough to require hospitalization for eight days. *S. derby* was pathogenic to 3 of 6 persons fed 15,000 000 organisms. The number that produced illness is in all cases within the range that might conceivably be encountered in the course of natural infection. The organisms were recovered from the stools of most of the men fed. Of greatest significance is the conclusive demonstration of a high incidence of excretion of organisms in the feces in the absence of symptoms. Volunteers given surprisingly small doses became asymptomatic excreters and carriers, and in some cases this situation persisted for months. On refeeding, the men who had become temporary carriers in the initial experiment, with one exception, failed to excrete the organisms. The volunteers were challenged at various intervals and dose levels. The illnesses that followed first or second refeeding were milder than the initial disease.[84] The data on symptoms demonstrate the prevalence of gastroenteritis and provide weighty proof that probably any salmonella can produce enteritis. In this respect these experiments support one aspect of the "Kiel doctrine,"[87, 88] which emphasizes the appearance of acute gastroenteritis after the ingestion of salmonella types not particularly adapted to man. The total doctrine is not tenable because it defends the notion that *S. paratyphoid B* causes typhoid-like syndromes exclusively. In the clinical reports by Seligmann and his colleagues[80] and by Edwards et al.[82] the symptoms of acute gastroenteritis were as frequent as in enteric fever. Not the parasite, but the variable host susceptibility and reactability are responsible for the varied clinical manifestations, the frequent extraintestinal localization and the small number of organisms required to initiate infection. This concept forms the basis of the so-called "Montevideo doctrine," which has received considerable support through the experimental salmonella infections in human beings.

Finally, these experiments recall the salmonella toxin hypothesis,[85, 89] which distinguished a bacterial type and a toxin type of food-borne salmonellosis. The form of illness that followed the ingestion of salmonellas was supposed to be largely determined by the ratio of preformed toxic metabolites to living bacilli ingested. Experimental work on mice, rats, rabbits, kittens and even monkeys, ably reviewed by Dolman[13] and by Elkeles,[90] demonstrated that suitably prepared filtrates or heat-killed cultures of some strains of certain salmonellas may contain factors toxic for mice, but not for monkeys. The crucial test of whether or not heat-stable products of the food-poisoning types of salmonella may cause illness in man is the feeding of such material to man. Only two reports could be traced of any conclusive experiments of this sort,[91, 92] and the results of these were negative. A two-year-old culture of *S. enteritidis* produced gastroenteritis when eaten by man in custards, but heated suspensions or filtrates of the culture after passage through the intestinal tract caused no symptoms. Furthermore, Hammerschmidt[93] presented epidemiologic evidence that only people who ate uncooked meat became ill. The evidence at hand favors the view that salmonella gastroenteritis is an infection and that the toxin type of food poisoning is probably attributable to the staphylococcus. However, in the pathogenesis of both infections, exotoxins, endotoxins, polysaccharides, proteins and lipid complexes released from the bacilli or cocci exert their toxic effects by causing inflammation of the mucous membrane, followed by corresponding violent reactions on the part of the infected patient. The mechanism of such effects is certainly not understood, it deserves pharmacologic and physiologic investigation. French physicians[19] continue to maintain that toxic and infectious factors are both involved in the acute, violent gastrointestinal attacks, particularly when meat is the vehicle.

Sources of Infection

Tracing the primary sources of salmonella in food poisoning has always been an exceedingly difficult problem. Buonomini[94] has made an effort to do so in relation to outbreaks in Italy. The distribution of these bacteria is universal. The natural habitat is the intestinal tract of animals and man.[55, 56] Food may contain the organisms because it has been contaminated at any stage of its preparation or processing, or it may already contain them because the

animal from which it came was infected with salmonellas, clinically or asymptomatically. Contamination is ultimately always traceable to the intestinal carrier, not to heavy invasion of tissue of visibly sick animals. Processing of food in bulk favors contamination of meat of many carcasses from the intestinal content of a single carrier animal.

Of the animals that furnish meat as the major source of salmonella gastroenteritis, poultry and pork are most frequently responsible. Edwards and his associates[92] and Barnes[93] and others believe that fowl constitute the greatest reservoir in the United States and that a high incidence of a given type in barnyard fowl in a certain locality is paralleled by a high incidence of the same type in man. A number of outbreaks have been attributed to ingestion of roast turkey, and bacterial studies indicate that these birds carry salmonellas more frequently than chickens do. Ducks, investigated as possible reservoirs during outbreaks in Great Britain, were frequently found to be excreting the organisms.[10] In recent years duck and hen eggs have been incriminated, with strong evidence in various outbreaks.[71, 72] Bacteriologic examination of 2132 samples of market eggshell scrapings has yielded 13 (0.6 per cent) cultures of *S. montevideo* and *anatum*. The shell, yolk and white may all contain salmonellas. Chicks hatched from infected eggs may be infected without signs of disease, and many may continue to carry the organisms. The incubator, with its increased moisture and temperature, constitutes one of the major problems in perpetuating this contamination. About 30 per cent of spray-dried egg powder from commercial powdered-egg factories has been positive for salmonella; contamination probably occurs from the shell, and multiplication is favored during the processing. Powders of low moisture content stored in the cold, are safer than those of high moisture content. Danger of infecting man arises when the reconstituted egg mixture is permitted to stand at temperatures above 15°C. where the bacteria can multiply.[98, 100]

As might be expected from the numerous isolations and wide variety of types of salmonella isolated from swine, contamination of pork was found in the retail market of a city in the United States. Of 250 samples of pork products, 13 (5.2 per cent) contained the organisms. The most probable source was the animals, pig (20 per cent) and ox, from which the meats were obtained. In the summary reports of Feig[1] meat and meat products were involved in 27.8 per cent, and poultry in 18.5 per cent of the 54 outbreaks of salmonella gastroenteritis. No particular meat product played a dominant role in the United States. The older statistics for continental Europe stress, in the following order, veal, beef, pork and horse meat.

Milk and milk products (14.8 per cent) and vegetables (13 per cent) have also been listed as vehicles, but the evidence on milk and milk products is not very sound. The large milk-borne outbreaks (130 cases) described by Conybeare and Thornton,[101] in which *S. dublin* was isolated from both the milk and the feces of one cow, is one of those rare occasions in which the mode of transfer from the animal reservoir to the human patient is clearly established. The statement that milk collected under sterile conditions never contains salmonella and the claims that cows secrete these organisms in milk are ambiguous. Many outbreaks were reported before the role of the healthy animal or human carrier was known. The importance of the use of eggs in milk products has not been taken into account. Synthetic cream may be contaminated through hen or duck egg albumin or through symptomless human excreters, as a recently reported explosive outbreak involving several hundred persons in Llanelly, Great Britain, amply illustrates.[102] Cream-custard bakery products carry their share (9 per cent of the outbreaks) of responsibility for salmonella outbreaks in England.

Why vegetables in the relatively high percentage of 13 per cent should play a role as vehicles and how they became contaminated cannot be determined from the sketchy histories readily available. The British reports, old[103] and recent,[104] list fruit, but not vegetables.

Rats and mice have been traditionally considered important in the spread of salmonellosis in man, but except for outbreaks traced to the use of "ratvirus" preparation for rodent extermination,[104, 105] the evidence is circumstantial.

Flies and roaches and other arthropods have been suspected as vehicles of the contaminants, and interesting experiments have been carried out to establish their role.[106] There is complete lack of direct evidence, but even if it could be furnished, arthropods surely play a minor part.

One of the latest developments in the salmonella field is the increasing interest in dogs and cats. In Australia a large outbreak was related, on epidemiologic grounds, to a preceding outbreak of *S. typhimurium* enteritis in cats,[107] obviously not a food-poisoning outbreak. The realization that pets and other animals not used for food may harbor salmonella in their intestinal tract creates problems not only for the veterinarian but also for the kennel keeper and the owner of the animals. In surveys of unselected groups of dogs or cats, 3 per cent had positive fecal cultures. In many kennels the feces of dogs were repeatedly cultured, the proportion of positive animals reaching 98 per cent.[108, 112] A total of 53 serotypes were encountered, including three new types, with the usual predominance — *S. anatum, rubislaw, oranienburg, senftenberg, newport, typhimurium* and *bredeney* — in the order listed. In the area where these studies were made, Florida, no evidence was obtained on which to judge the epidemiologic significance to man of salmonella infection of family dogs. But wherever the intestinal

carrier stage is widespread, the potential danger of contamination of food is obviously present.

Human beings infected through animals may, during illness and for varying periods thereafter, discharge pathogenic bacilli in their feces and contaminate food by handling. The importance of the human being in comparison to the animal as a source of infection has still to be defined. The diligently collected observations in Great Britain stress more forcibly than formerly the contamination of food by man. During 1949, at least 5 outbreaks were caused by known, persistent symptomless human excreters, and in 21 others the organism was isolated from food handlers or other symptomless carriers who might have been responsible for dissemination of the infection. In most of these it was impossible to decide whether the symptomless carriers were actually the cause of the outbreak or the victims of it. In carefully studied family outbreaks, 167 persons had symptoms, and 172 were symptomless carriers.[11] Six of 17 food poisoning outbreaks in Massachusetts were due to infection by human contact.[113] As long ago as 1943, Dolman,[12] impressed by the high incidence of salmonella carriers in food handlers, had noted that the excretion of the organisms may continue longer after food-borne salmonella infection than had generally been believed. This is certainly borne out in the experimental studies in human beings. In a carefully studied explosive outbreak of *S. typhimurium* food poisoning affecting several hundred persons, not only patients but also symptomless carriers shed the causative agent for as long as nine weeks. The percentage of persons still excreting *S. typhimurium* after various intervals followed a logarithmical law: 47 per cent of those excreting the organisms at the end of a week had ceased doing so by the end of the following week.[102]

Findings such as these clearly demand that systematic stool cultures of food handlers be made and thus confer on the laboratory a considerable responsibility in preventing transmission of salmonella infection from man to man through the intermediacy of food. They re-emphasize the role of symptomless human carriers and animal reservoirs in the epidemiology of this type of gastroenteritis. Each should be given due consideration.

Prevention and Control

As important steps in reducing the high incidence of gastroenteritis, hygienic and other preventive measures are essential. Probably in no more detail has the relevant matter been presented and discussed than in Chapter 7 of the scholarly book by Dewberry.[3] Little can be added except the warning that, despite all precautions of the manufacturer, dealer, food handler and food official, the ultimate responsibility for preventing single or group outbreaks rests squarely on those who handle food in the public or domestic kitchen and prepare it for the table.

The obligations of food handlers are as follows: food to be eaten raw must be fresh and free from stale odors and from soft or decomposed areas and must be thoroughly cleaned and washed in drinking water; secondly, sound food must be thoroughly cooked in small pieces and long enough to heat the center of the pieces, use of thermometers in restaurant and institution kitchens being of real value (duck eggs may be disinfected with a boiling-hot solution of 10 per cent sodium carbonate[114] and should be boiled for fourteen minutes,[115] only coagulation of the yolk assuring protection); soft-cooked foods, if not eaten promptly, must be refrigerated or recooked before serving, even if signs of spoilage are not evident; and reconstituted egg powders should be cooked immediately and thoroughly after reconstitution.

Streptococcal Gastroenteritis

Reports of outbreaks of food poisoning clinically and epidemiologically indistinguishable from staphylococcal gastroenteritis appear with increasing frequency. Enormous numbers of alpha-hemolytic streptococci — *Str. faecalis* — have been found, both here and abroad, in this third group of outbreaks of varying severity, in food from which neither staphylococci nor salmonellas could be cultivated. Whenever the incubation time is two to eighteen hours (median, six to ten and three tenths hours)[1] and the laboratory finds several million organisms (mostly *Str. faecalis*) per gram of the suspected food, reporting this episode as streptococcal gastroenteritis may be justified. How often these two specifications have really been met is conjectural. The annual reports from 1945 to 1947 list 34 outbreaks, of which 21 were attributed to food articles (turkey, pastries and potato salad) contaminated with mixed flora; of these 21, 17 included staphylococci, and 2 salmonellas.

The food-poisoning potentialities of the different bacteria have been judged by the numerical, not the qualitative, predominance in the suspected food. Equally unsatisfactory is the identification of the streptococci: in half the outbreaks in America the type is not specified or such meaningless descriptions as nonhemolytic, hemolytic or alpha-hemolytic streptococci or *Str. viridans* have been used. The British reports are equally indefinite. Until more exhaustive bacterial analyses accompany the reports, the actual prevalence of food-borne illnesses caused by these organisms cannot be estimated with any degree of certainty.

The California State Department of Public Health listed 3 outbreaks (210 cases) probably caused by streptococci among a total of 54 outbreaks for that state in 1952. In 2 of the 3, *Str. faecalis* was found in chili sauce and coconut-cream pie, respectively, and in 1, a mixture of streptococci

and staphylococci was cultured from the incriminated food. These figures, together with those for the preceding nine years, bring the total to 7 (3 per cent) of 253 outbreaks. Streptococcal gastroenteritis certainly seems to be much less prevalent than the other two kinds discussed.

Outbreaks should be attributed to streptococci only if they are proved to be present in large numbers in the incriminated food and have been identified as *Str. faecalis*.

As far as is known this illness has never been fatal.

Before 1948 results of experimental *Str. faecalis* food poisoning were equivocal. One group reported abdominal distress, cramps and diarrhea in 5 of 7 volunteers who ingested "reasonable doses" of several strains implicated in 2 outbreaks of food poisoning.[116] Another worker reported failure to produce symptoms in any of 4 volunteers, each of whom was given a meat pie heavily infected with *Str. faecalis* of food-poisoning origin.[13] The most recent human experiments, by Buchbinder and his colleagues,[117] may explain the contradictions.

To learn anything decisive from such experiments, individual susceptibility must be accommodated by the use of a large number of volunteers, the concentration of toxic metabolites at the different growth phases must be established, and the interval between isolation of the organisms from the suspected food and the test on volunteers must be short. Fulfilling these conditions, Buchbinder and his group[117] found that *Str. faecalis* may play a decisive role. Symptoms of acute gastric or intestinal disturbance or both were produced in 6 (possibly 7) of 26 volunteers who ate foods in which this organism had grown for only five hours. Similar symptoms did not follow ingestion of twenty-hour cultures. In the cases in which they did occur, symptoms began after an incubation period of two and a half to ten hours and persisted for twelve to thirty-seven hours. The course was afebrile. The concentration of *Str. faecalis* that produced symptoms ranged from 22.7×10^9 to 148×10^9 organisms, the same order as that required to produce gastroenteritis with *Staph. aureus*.

Similar observations were made independently by Moore,[118] who fed not only an artificially inoculated chocolate pudding but also living cultures and filtrates to a volunteer. The strain used was isolated from a chocolate pudding that had caused 153 cases of food poisoning among 309 children. Symptoms of acute gastroenteritis developed that were quite similar to those in the outbreak during which the strain was isolated. They appeared after a similar incubation period, three to six hours. Diarrhea was severe in the eighteenth hour. Oral administration of a suspension of washed streptococci in Ringer's solution had no effect on the volunteer.

The clinical manifestations are those of an illness produced by a preformed heat-stable toxin. Its nature is not known; it may be tyramine released by decarboxylation of tyrasine by *Str. faecalis*.[119, 120] One would like to know if only certain types may form potent toxins in a suitable environment, as in staphylococcal food poisoning. The decisive confirmation of the role of *Str. faecalis* would provide a valuable solution to many of the problems of food poisoning.

Shigella Gastroenteritis

Since bacillary dysentery is probably the most important cause of endemic acute diarrhea, it is not surprising that it appears in the lists of food-borne infections. Again, improved diagnostic procedures, particularly the preservation of stool specimens for shipment, has increased the chances of bringing these infections to light. Shigellas were identified in 14 of the 476 outbreaks repeatedly mentioned in this report.[1] Although the organisms are involved in only 2.9 per cent of all outbreaks, the total number of victims (2883) is nearly as great as that reported for salmonella poisonings. Two outbreaks transmitted by water were included in the Feig tabulations as food poisoning. Two were listed as gastroenteritis, and 1 as diarrhea. *Shigella paradysenteriae* was identified in 9, *S. sonnei* in 3, *S. alkalescens* in 1, and an unspecified type in 1. In the 88 outbreaks due to organisms other than staphylococci or salmonellas, the British reports list only 4 outbreaks due to shigella, all due to *sonnei*. Both in the United States and in Great Britain the *paradysenteriae* and *sonnei* species are the predominant ones.[121]

Outbreaks that may masquerade as food poisoning are merely segments of the over-all problem of diarrheal disease that is prevalent in urban or rural areas not modern in a sanitary sense. The reservoir of the shigella is the human carrier, and the safe removal of his excreta will protect not only the water but also the foods such as milk that serve as vehicles.

The newer knowledge of shigellosis, well reviewed by Hardy and Watt,[122] should be consulted for further details.

The time has arrived to report outbreaks of definitely proved shigella gastroenteritis as such or as shigellosis, not as food poisoning. The relatively long incubation period, the clinical manifestations and epidemiologic pattern are sufficiently distinct to prevent future confusion of this disease with staphylococcal or salmonella gastroenteritis. What is known about shigellosis in general applies to the same illness whether conveyed in water or in food.

(To be concluded)

References

49. Meyer, R. Zur Statistik der Fleischvergiftung im Jahre 1948. *Monatschr. f. Veterinar.* 8:13-15, 1948.
50. Seligmann, E., Saphra, I., and Wassermann, M. Salmonella infections in U. S. A.: second series of 2000 human infections recorded by New York Salmonella Center. *J. Immunol.* 54:69-87, 1946.
51. Seligmann, E., and Saphra, I. New salmonella type: Salmonella waycross. *J. Bact.* 55:561-563, 1948.

52. Edwards, P. R., Bruner, D. W., and Moran, A. B. Further studies on occurrence and distribution of salmonella types in United States. *J. Infect. Dis.* **83**:220-231, 1948.

53. Felsenfeld, O., and Young, V. M. Study of human salmonellosis in North and South America. *Am. J. Trop. Med.* **29**:483-491, 1949.

54. Bynoe, E. T., Bailey, W. R. A., and Laidley, R. A. Salmonella types in Canada. *Canad. J. Pub. Health* **44**:137-147, 1953.

55. Taylor, J. Discussion on food poisoning. *Proc. Roy. Soc. Med.* **42**: 219, 1949.

56. Smith, H. W., and Buxton, A. Isolation of salmonellae from faeces of domestic animals. *Brit. M. J.* **1**:1478-1483, 1951.

57. Conybeare, E. T. Discussion on food poisoning. *Proc. Roy. Soc. Med.* **42**:214-216, 1949.

58. Gärtner. Über die Fleischvergiftung in Frankenhausen a. K. und den Erreger derselben. *Breslau. aerztl. Zeschr.* **10**:249-252, 264-268, 277-280, and 292, 1888.

59. *Idem.* Über die Fleischvergiftung in Frankenhausen a. K. und den Erreger derselben. *Corr.-Bl. d. allg. ärztl. Ver. v. Thüringen* **17**: 573-600, 1888.

60. van Ermengem, E. Recherches sur des cas d'accidents a'imentaires produits par des saucissons. *Rev. d'hyg. et de police sanit.* **18**:761-819, 1896.

61. De Nobele, J. Du séro-diagnostic dans les affections gastro-intestinales d'origine alimentaire. *Ann. Soc. de méd. de Gand* **77**:281-306, 1898.

62. Noyes, A. Isolation of pathogens in suspected food poisoning. *Am. J. M. Technol.* **17**:302-305, 1951.

63. Savage, W. G. *Food Poisoning and Food Infection.* 247 pp. Cambridge: University Press, 1920.

64. Neely, R. A., and Nelson, M. G. Salmonella food poisoning due to duck eggs with trial of chloramphenicol on carrier state. *Month. Bull., Ministry of Health & Pub. Health Lab. Serv.* **10**:96-101, 1951.

65. White, P. B. *Further Studies of the Salmonella Group.* (Med. Res. Council, Spec. Rep. Series, No. 103.) 160 pp. London: His Majesty's Stationery Office, 1926.

66. Kauffmann, F. *Diagnosis of Salmonella Types.* 86 pp. Springfield, Illinois: Charles C Thomas, 1950.

67. *Idem.* Fifth report on salmonella group. Paper read at the International Congress of Microbiology, Rome, 1953.

68. Van Oye, E. Les salmonellae du Congo Belge. *Ann. Soc. belge de méd. trop.* **32**:179-202, 1952.

69. *The Bacteriology of Spray-Dried Egg with Particular Reference to Food Poisoning.* (Med. Res. Council, Spec. Rep. Series, No. 260.) 66 pp. London: His Majesty's Stationery Office, 1947.

70. Zeman, W. Eine Paratyphus-C Gastroenteritis durch den Genuss von Trockeneipulver. *Deutsches med. Wchnschr.* **74**:121, 1949.

71. Watt, J. Outbreak of salmonella infection in man from infected chicken eggs. *Pub. Health Rep.* **60**:833-839, 1945.

72. Crowe, M. Localized outbreak of salmonella food poisoning apparently transmitted by hen's egg. *J. Hyg.* **44**:342-345, 1946.

73. Bernstein, A. Salmonella infection of hen eggs. *Month. Bull. Ministry of Health & Pub. Health Lab. Serv.* **11**:64-67, 1952.

74. Gordon, R. F., and Buxton, A. Case of food-poisoning in man, probably caused by consumption of duck egg. *Month. Bull. Ministry of Health & Pub. Health Lab. Serv.* **5**:46-50, 1945.

75. Murdock, C. R., and Gordon, W. A. M. Incidence of *Salmonella* in healthy carrier state in Northern Ireland. *Month. Bull., Ministry of Health & Pub. Health Lab. Serv.* **12**:72-76, 1953.

76. Trüb, C. L. P., and Schneider, P. Auftreten gehäufter Einzelerkrankungen und Gruppenerkrankungen durch Salmonella panama und Salmonella-Typen der Paratyphus C-Gruppe im Lande Nordrhein-Westfalen 1950-1951. *Ztschr. f. Hyg. u. Infektionskr.* **135**:121-145, 1952.

77. Bahr, L. Einige Untersuchungen über die Virulenzverhältnisse eines zur Paratyphusbazillengruppe gehörenden Bakteriums (Erste Mitteilung). *Ztschr. f. Infektionskr. d. Haustiere* **27**:237-275, 1925.

78. *Idem.* Einige Untersuchungen über die Virulenzverhältnisse eines zur Paratyphusbazillengruppe gehörenden Bakteriums (Zweite Mitteilung). *Ztschr. f. Infektionskr. d. Haustiere* **30**:273-291, 1927.

79. Dack, G. M., Jordan, E. O., and Wood, W. L. "Food poisoning" produced in monkeys by feeding living Salmonella cultures. *J. Prev. Med.* **3**:153-158, 1929.

80. Mallmann, W. L., Ryff, J. F., and Matthews, E. Studies on Salmonella group — methods of isolation and pathogenicity of strains occurring in intestines of chickens. *J. Infect. Dis.* **79**: 253-262, 1942.

81. Hormaeche, E., Peluffo, C. A., and Aleppo, P. L. Las salmonelas en patologia infantil. *Arch. de pediat. d. Uruguay* **11**:8-28, 1940.

82. McCullough, N. B. Relative pathogenicity of certain salmonella strains for man and mice. *Pub. Health Rep.* **66**:1538-1540, 1951.

83. McCullough, N. B., and Eisele, C. W. Experimental human salmonellosis. I. Pathogenicity of strains of *Salmonella meleagridis* and *Salmonella anatum* obtained from spray-dried whole egg. *J. Infect. Dis.* **88**:278-289, 1951.

84. *Idem.* Experimental human salmonellosis. II. Immunity studies following experimental illness with *Salmonella meleagridis* and *Salmonella anatum*. *J. Immunol.* **66**:595-606, 1951.

85. *Idem.* Experimental human salmonellosis. III. Pathogenicity of strains of *Salmonella newport, Salmonella derby* and *Salmonella bareilly* obtained from spray-dried whole egg. *J. Infect. Dis.* **89**:207-213, 1951.

86. *Idem.* Experimental human salmonellosis. IV. Pathogenicity of strains of *Salmonella pullorum* obtained from spray-dried whole egg. *J. Infect. Dis.* **89**:259-265, 1951.

87. Bitter, L. Über den klinischen Verlauf der durch Paratyphus B- und Enteritis-Breslau-Bakterien bedingten Erkrankungen. *Ztschr. f. Hyg. u. Infektionskr.* **100**:347-349, 1923.

88. Gärtner, W. Kann der Paratyphus B abdominalis in klinischer, pathologischanatomischer, epidemiologischer und bakteriologischer Hinsicht von der sogenannten Gastroenteritis paratyphosa B abgetrennt werden? *Centralbl. f. Bakt., Abt.* 1, *orig.* **87**:486-525, 1921-1922.

89. Savage, W. G. *Canned Food in Relation to Health.* 146 pp. Cambridge: University Press, 1923.

90. Elkeles, G. Paratyphus, Fleischvergiftung und ihre Beziehungen zueinander. *Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap.* **11**:68-219, 1930.

91. Dack, G. M., Cary, W. E., and Harmon, P. H. Unsuccessful attempt to produce Salmonella intoxication in man. *J. Prev. Med.* **2**:479-485, 1928.

92. Verder, E., and Sutton, C. Is salmonella food poisoning caused by living bacilli or by thermostabile toxic products? *J. Infect. Dis.* **53**:262-271, 1933.

93. Hammerschmidt, J. Beobachtungen bei Fleischvergiftungsepidemien. *Wien. klin. Wchnschr.* **48**:325-327, 1935.

94. Buonomini, G. Le salmonellosi nel quadro delle tossinfezioni alimentari. *Ann. d. san. pub.* **9**:1591-1701, 1948.

95. Barnes, L. V. A. Pathogenic enteric bacilli. II. Salmonella group. *U. S. Nav. M. Bull.* **43**:939-949, 1944.

96. Wilson, J. E. Infected egg shells as means of spread of salmonellosis in chicks and ducklings: preliminary note. *Vet. Rec.* **57**:411-413, 1945.

97. Gibbons, N. E., and Moore, R. L. Note on artificially infected fowl as carriers of salmonella. *Poultry Sc.* **25**:115-118, 1946.

98. Buxton, A., and Gordon, R. F. Epidemiology and control of *Salmonella thompson* infection of fowls. *J. Hyg.* **45**:265-281, 1947.

99. Solowey, M., McFarlane, V. H., Spaulding, E. H., and Chemerda, C. Microbiology of spray-dried whole egg. II. Incidence and types of Salmonella. *Am. J. Pub. Health* **37**:1571-1582, 1947.

100. Solowey, M., Rosenstadt, A., Spaulding, E. H., and Chemerda, C. Occurrence of multiple salmonella types in spray dried whole egg powder. *Poultry Sc.* **27**:12-16, 1948.

101. Conybeare, E. T., and Thornton, L. H. D. *Report on Outbreak of Food Poisoning Due to Salmonella, Type "Dublin" and Conveyed by Raw Milk. (Report on Public Health and Medical Subjects, No. 82.)* 8 pp. London: His Majesty's Stationery Office, 1938.

102. Kwantes, W. Explosive outbreak of Salmonella typhi-murium food poisoning in Luneiby. *Month. Bull., Ministry of Health & Pub. Health Lab. Serv.* **11**:239-248, 1952.

103. Savage, W. G., and White, P. B. *Food Poisoning: Study of 100 Recent Outbreaks.* (Med. Res. Council, Spec. Rep. Series No. 92.) 112 pp. London: His Majesty's Stationery Office, 1925.

104. Leslie, P. H. Bacteriological classification of principal cultures used in rat and mouse control in Great Britain. *J. Hyg.* **42**:552-562, 1942.

105. Dathan, J. G., McCall, A. J., Orr-Ewing, J., and Taylor, J. Salmonella enteritidis infection associated with use of anti-rodent "virus." *Lancet* **1**:711-713, 1947.

106. Ostrolenk, M., and Welch, H. House fly as vector of food poisoning organisms in food producing establishments. *J. Am. Pub. Health* **32**:487-494, 1942.

107. Mackerras, M. J., and Mackerras, I. M. Salmonella infections in Queensland. *Australian J. Exper. Biol. & M. Sc.* **27**:163-171, 1949.

108. Wolff, A. H., Henderson, N. D., and McCallum, G. L. Salmonella from dogs, and possible relationship to salmonellosis in man. *Am. J. Pub. Health* **38**:403-406, 1948.

109. Galton, M. M., Scatterday, J. E., and Hardy, A. V. Salmonellosis in dogs. I. Bacteriological, epidemiological and clinical considerations. *J. Infect. Dis.* **91**:1-5, 1952.

110. Stucker, C. L., Galton, M. M., Cowdery, J., and Hardy, A. V. Salmonellosis in dogs. II. Prevalence and distribution in greyhounds in Florida. *J. Infect. Dis.* **91**:6-11, 1952.

111. McElrath, H. B., Jr., Galton, M. M., and Hardy, A. V. Salmonellosis in dogs. III. Prevalence in dogs in veterinary hospitals, pounds and boarding kennels. *J. Infect. Dis.* **91**:12-14, 1952.

112. Mackel, D. C., Galton, M. M., Gray, H., and Hardy, A. V. Salmonellosis in dogs. IV. Prevalence in normal dogs and their contacts. *J. Infect. Dis.* **91**:15-18, 1952.

113. Rubenstein, A. D., Feemster, R. F., and Smith, H. M. Salmonellosis as public health problem in wartime. *Am. J. Pub. Health* **34**: 841-853, 1944.

114. Knothe, H., and Budach, F. Bakteriologische Untersuchungen über die Bedeutung des Enterecis als Erreger von bakterriellen Nahrungsmittelvergiftungen. *Ztschr. f. Hyg. u. Infektionskr.* **134**:574-593, 1952.

115. Clarenburg, A., and Burger, H. C. Survival of salmonellae in boiled ducks' eggs. *Food Research* **15**:340, 1950.

116. Cary, W. E., Dack, G. M., and Myers, E. Institutional outbreak of food poisoning possibly due to streptococcus. *Proc. Soc. Exper. Biol. & Med.* **29**:214, 1931.

117. Buchbinder, L., Osler, L. G., and Steffen, G. I. Studies in enterococcal food poisoning. I. Isolation of enterococci from foods implicated in several outbreaks of food poisoning. *Pub. Health Rep* **63**:103-118, 1948.

118. Moore, B. Food-poisoning outbreak apparently caused by α-haemolytic streptococci. *Month. Bull., Ministry of Health & Pub. Health Lab. Serv.* **7**:136-145, 1948.

119. Sherman, J. M. Streptococci. *Bact. Rev.* **1**:1-97, 1937.

120. Sherman, J. M., Mauer, J. C., and Stark, P. Streptococcus fecalis. *J. Bact.* **33**:275-282, 1937.

121. Weil, A. J. Dysentery: progress report for years 1942 to 1946. *J. Immunol.* **55**:363-405, 1947.

122. Hardy, A. V., and Watt, J. Communicable diseases with predominant enteric manifestations. In: *Communicable Diseases.* 1035 pp. Edited by R. L. Pullen. Philadelphia: Lea & Febiger, 1950. Pp. 825-850.

MEDICAL INTELLIGENCE

WORLD MEDICAL ASSOCIATION

Seventh General Assembly

THE Seventh General Assembly of the World Medical Association, held at The Hague during the first week of September, 1953, considered an agenda containing a number of matters of interest to the world medical profession. Prominent among these matters were the reports of the four regional secretaries of the organization: S. C. Sen, of India, representing Asia; J. G. Hunter, of Australia, representing Australasia; Paul Cibrie, of France, representing Europe; and J. A. Bustamante, of Cuba, representing Latin America. Since the secretary-general, Dr. Louis Bauer, maintains the secretariat of the Association in New York, all the corners of the earth outside of those dominated by the Soviet Union may thus be assumed to be represented.

These reports dealt largely with the social-security problems of the regions involved and presented in some detail the difficulties that the profession is having with the governments of the countries included in these regions. Two points became apparent: one was that the definition of social security seems in some areas to represent what we are inclined to call socialized medicine; the other was that certain delegates to the Assembly seemed in this respect interested rather in the welfare of the doctor than in the quality and extent of the services that he might render. It is natural, human and necessary that the rights of the physician should be protected and his reward to some degree guaranteed, and to this extent in a world as confused as the one that man presently inhabits, organizations of physicians must take over some of the functions of trade unions so far as that is consistent with the dignity and the ideals of the profession. But in all other respects the obligations that the physician has so willingly assumed impose on him the primary role of the dispenser of service rather than that of the recipient of its rewards.

This tendency of the discussion to center itself about the welfare of the physician was noted by others and was brought to the attention of the Assembly by T. Rowland Hill, of Great Britain. Dr. Hill raised the question whether, with all deference to the struggle of the physician to maintain economic independence and social prestige, he is not nevertheless thinking too much of his own interests and losing sight of his professional dedication to service. His efforts in the direction of social security, according to Hill, should be directed rather toward providing service for those who cannot afford it than securing protection for himself. Along the same line Batkin, of South Africa, noted that only 2 paragraphs in the report under discussion referred to the patient, the other 10 being in the interests of the physician. The point was brought out by Gundersen, of the United States delegation, that in this country physicians and other professional workers are trying to keep out of Social Security and slow down the drift toward the welfare state. As aptly expressed at this juncture by Dag Knutson, of Sweden, chairman of the Council of the Association, what is sauce for the goose is sauce for the gander, and the welfare of doctor and patient are after all closely integrated. In general it is fair to say that the deliberations of the Assembly seemed to be pervaded with a becoming spirit of altruism.

Long discussion was evoked by the suggestion of the Committee on Planning and Finance that more regional meetings be held, similar to the Western Hemisphere meeting held at Richmond, Virginia, last April, and that a general assembly in 1955 be omitted. The discussion departed from its course to become an argument concerning the advisability of abandoning general assemblies in favor of regional meetings, which was actually not the question at all. Nevertheless many voices were raised in defense of the annual assembly with not a few expressions in favor of holding various regional meetings and a general assembly in alternate years. The popular opinion seemed to be that frequent general assemblies are necessary to preserve the world-wide character of the Association, despite the amount of travel required for attendance, especially on the part of those delegates living at great distances from Europe, where a majority of the assemblies are likely to be held.

Among other matters discussed was the formation in Brussels last June of the International Union of the Medical Press, inspired by a group of editors of Belgium, France and Italy. An outgrowth of, or a successor to, the International Association of the Medical Press, which has existed for some years in France and Italy, membership in it is open to the editors and publishers of the journals of all national medical associations, which seem automatically to exclude state, sectional or independent publications. The Assembly took the obvious and reasonable action of voting to co-operate with the new Union, which in turn has indicated a desire to co-operate in making successful the meeting of editors held in conjunction with the Annual Assembly of the World Medical Association. Perhaps it is not too much to hope that at some time there may be an international council of the medical press under the auspices of the WMA, in which the International Union may play an important part.

Another notable action taken at this seventh assembly was the admission to membership in the World Medical Association of three additional national medical associations, raising the total representation to 46. The new members are Brazil, Indonesia and Lichtenstein. The last mentioned met with some opposition from certain quarters, since the medical association of Lichtenstein consists of only 11 members, who will, under the rules of the Association, send as many delegates to the Assembly as the American Medical Association. The Lichtenstein Association, however, meets all the established qualifications for membership.

Dr. A. Spinelli, of Italy, was chosen president-elect and to him Dr. Hulst of the Netherlands, the current president, will hand the gavel at Rome next year.

The last item of the Assembly was the semi-independent all-day meeting of medical editors on September 8, the Monday after the Saturday on which the Assembly itself came to a close. This meeting, with some 75 persons in attendance, was held in the same medieval "Ridderzaal" or Knights Hall, in the center of the Dutch government buildings, in which the Assembly had taken place. Under the chairmanship of Dr. A. Plichet, of France, six papers were presented at the meeting: "Obituaries As Contemporary Medical History," by Dr. J. Van Lennep, editor of *Le Medicine Belge*; "The Function of a General Medical Journal," by the editor of the *New England Journal of Medicine*; "Medical Documentation," by Dr. Hugh Clegg, editor of the *British Medical Journal*; "The Responsibility of the Author and Editor in Preparing A Manuscript for the Press," by Dr. J. Björneboe, editor of the Norwegian *Tidskrift For Den Norske*; and two papers on "Relations Between the Medical and Non-Medical Press," by Dr. Charles Mayer, of Belgium, and Mr. John Pringle, public-relations officer of the British Medical Association.

In this conference much was said about the volume of medical literature clamoring to be released, and the mutual obligation of author and editor to make it not only comprehensible but literate. Mention was also made of the keen competition that exists among the many current journals for enough readers to justify their existence, W. R. Feasby, editor of *Modern Medicine of Canada and Ontario Medical Review*, appropriately terming it the battle of communication, and calling attention to changing reading habits, which have included the popularization of contributions concerning medical economics.

In closing, a word must be said about the magnificent hospitality extended by the Royal Netherlands Medical Association to the delegates and observers and their families. This included, in addition to separate activities for the ladies, a dinner at which some 600 persons were seated, a reception tendered by the Netherlands National Government and the government of the City of The Hague, an excursion to Amsterdam, including a reception tendered by the mayor of that city, an excursion to Rotterdam with a similar reception, and a luncheon for attendants at the editors' meeting, including their auxiliary personnel, tendered by the Nepera Chemical Company.

FULMINANT HEPATITIS DURING TREATMENT WITH PROPYLTHIOURACIL*

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THE effectiveness and relative lack of toxicity of propylthiouracil have made it valuable in the treatment of thyrotoxicosis. Untoward reactions, especially granulocytopenia, rarely hepatic injury, were encountered frequently with its predecessor, thiouracil. However, hematologic changes with propylthiouracil have proved so unusual that some clinicians consider periodic blood counts an unnecessary precaution during therapy.[1] Abandonment of such a safeguard is to be decried since other authors[2-4] report as high as a 2 to 4 per cent incidence of toxic reactions with propylthiouracil. In 1651 treated cases granulocytopenia occurred in 19.[4] The literature contains several reports of liver damage in patients receiving propylthiouracil. Livingston and Livingston[5] have recorded hepatocellular jaundice and agranulocytosis that followed the administration of propylthiouracil for six weeks, with subsequent recovery on cessation of therapy. In the case of agranulocytosis after propylthiouracil therapy presented by Juliar and Harris[6] terminal jaundice is mentioned, with no qualification regarding its type. Autopsy was not performed. Colwell, Sando and Lang[7] described a fatal case of agranulocytosis combined with jaundice that developed after four weeks of treatment. The liver of this patient at autopsy displayed some loss of cellular architecture in the central portion of the lobules, a finding interpreted by the investigators as evidence of early toxic hepatitis.

The present report deals with fulminant hepatitis developing after the administration of only 300 mg. of propylthiouracil during one day.

CASE REPORT

A 52-year-old unmarried woman was first seen 6 months before admission. At that time, she had obvious hyperthyroidism. She was agitated, had tremors and a rapid pulse, and had lost an unspecified number of pounds. The basal metabolic rate was +45 per cent. She improved considerably with Lugol's solution, and after 3 months the basal metabolic rate fell to +9 per cent. She was seen for further evaluation 1 week before admission. Though she was in good health and able to perform the difficult duties of a legal secretary, there was some evidence of nervousness, suggestive of hyperthyroidism. No objective tests were

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made at this time. Because of the possibility that she had become refractory to iodine, a course of propylthiouracil was suggested for more complete preparation before subtotal thyroidectomy. She was given 300 mg. of the drug in divided doses during 1 day, after which explosive effects rapidly developed. On the following day she was violently ill, with diffuse abdominal pain and frequent vomiting. These symptoms increased during the next 2 days. She had no fever. On admission to the hospital on the 4th day of her illness she was in shock, with a rapid, weak pulse and a temperature of 97°F. by rectum. Abdominal pain and tenderness were diffuse. There was moderate distention, but no localizing signs could be elicited.

Because she had no bowel movements, x-ray examination of the abdomen was carried out, revealing considerable gas in the small and large intestine, but nothing to suggest obstruction. Examination of the blood showed a red-cell count of 4,170,000, with a hemoglobin of 9.6 gm. per 100 cc., and a white-cell count of 27,700, with 85 per cent neutrophils, 13 per cent lymphocytes and 2 per cent monocytes. There were no atypical cells in the smear, and platelets were seen in normal distribution. The urine contained a small amount of albumin, with a few granular casts, but no bile. A microprecipitation test for syphilis was negative. No additional laboratory studies could be made, since the patient survived for only 8 hours after admission. She was examined by a surgical consultant, who believed he was dealing with an acute surgical emergency, but her rapid deterioration precluded intervention. She was given 500 cc. of 5 per cent glucose in saline solution intravenously, as well as oxygen, penicillin and streptomycin. Blood transfusion had been started, but she died after receiving only 100 cc.

FIGURE 1. *Section of the Liver, Showing Necrotic Central Halves of Liver Lobules and Infiltration with Polymorphonuclear Leukocytes (X 68).*

At autopsy, performed 3 hours after death, the peritoneal cavity contained 200 cc. of thin, blood-tinged fluid, but there was no inflammatory exudate. The stomach and intestines were moderately distended. No intrinsic or extrinsic obstructing lesion could be found. The stomach contained 300 cc. of dark-brown fluid, and the bowel to the hepatic flexure was filled with blood-tinged liquid material. The terminal colon was relatively empty except for bloody mucus. No single source of gastrointestinal hemorrhage could be found, though the mucous membrane from the distal end of the stomach to the 1st portion of the colon was edematous and hemorrhagic. Microscopically, these areas merely showed engorgement of vessels in the wall and scattered polymorphonuclear leukocytes on the serosa.

The liver weighed 1100 gm., and the only possible clue grossly to the extensive alterations subsequently revealed under the microscope was an irregular, yellow mottling of the organ. Microscopical examination, however, disclosed severe damage. Massive disintegration of the central halves of all liver lobules was evident (Fig. 1). In these areas, residual parenchymal cells could be identified only as eosinophilic shadows around which many pyknotic nuclear remnants and polymorphonuclear leukocytes were visible. The peripheral halves of the lobules and periportal zones were spared. The extrahepatic biliary system was normal.

The spleen weighed 250 gm. It was pink gray and soft and had irregular yellow hemorrhagic zones 1 or 2 cm. in width. Microscopically, these zones consisted of focal areas of necrosis of pulp substance. The follicles were well retained.

The thyroid gland had the characteristic appearance of an iodinized, hyperactive gland. It was not enlarged and was of normal consistence, but microscopical examination showed zones of residual hyperplasia alternating with normal acini. Scattered lymphocytes were evident in the stroma. The kidneys were unaltered.

DISCUSSION

The diagnosis of acute hepatitis in this patient was established only after post-mortem discovery of two striking alterations in the liver: massive destruction of hepatic cells, and extensive inflammatory changes in the organ. The lesions seen microscopically were not suspected particularly in view of the minimal grossly evident alterations. The acute hepatic disease was undoubtedly responsible for the ascites, splenic necrosis and gastrointestinal bleeding found at autopsy. Unfortunately, laboratory analyses were limited in this patient, but there can be little doubt that hypoprothrombinemia had existed to account for the hemorrhagic tendency. Jaundice was not evident clinically, and no bile had been present in the urine. Lucké and Mallory,[8] in their review of the fulminant form of epidemic hepatitis in military personnel, stated that jaundice, on the average, appeared during the second or third day after the onset of symptoms, and bile in the urine on the third or fourth day.

Several possibilities for the etiology of the hepatic lesion must be considered:

So-called Epidemic Acute Hepatitis

The fulminant form described by Lucké and Mallory[8] has a clinical picture not unlike that in the case reported above. In 133 cases reviewed, the authors found 2 patients who lived two days, and 36 patients who survived three to five days. Microscopically, destruction of the livers in such rapidly fatal cases was almost total (this was not so in the case under discussion). Furthermore, the fulminant cases among military personnel occurred in epidemic form, whereas the isolated occasional example of acute hepatitis encountered now in the civilian population is mild and rarely fatal, most frequently terminating in full recovery several weeks after the onset of jaundice. A diagnosis of fulminant epidemic hepatitis of viral origin, therefore, does not appear tenable.

Liver Necrosis of Hyperthyroidism

Hyperthyroid patients who succumb to a fatal thyroid crisis may have hepatic lesions. These have been clearly described by Lord and Andrus[9] and McIver.[10] They may be identical with the changes encountered in the case described above. However, such patients usually die in an obviously

hyperthyroid state, most commonly during or immediately after thyroidectomy. These circumstances were not present in the case under discussion.

Liver Lesion from Shock Secondary to Gastrointestinal Hemorrhage

Moon[11] described extensive hepatic necrosis in patients dying from shock. The patient discussed above lapsed into a state of shock, probably as a terminal manifestation of extensive damage to the liver. There was no single source of hemorrhage from the gastrointestinal tract; rather, a general ooze was noted that was probably secondary to prothrombin deficiency — it was certainly not of sufficient magnitude to produce a significant anemia. Shock, therefore, does not appear to be the motivating force of the hepatic necrosis in this patient.

Toxic Effect of Propylthiouracil

Circumstantial evidence is most persuasive that the hepatic lesions were produced by propylthiouracil, although only 300 mg. was taken during one day. The onset of a rapidly ensuing fatal syndrome one day after administration of the drug with no other apparent reason is strongly suggestive of some hypersensitivity. As completely as could be determined, the patient had not been exposed to any potential hepatotoxic agents such as volatile materials or other drugs, and had consumed only the prescribed dose of propylthiouracil.

Summary

A case of fulminant hepatitis that followed the administration of only 300 mg. of propylthiouracil in one day is described.

References

1. McCullagh, E. P., Hibbs, R. E., and Schneider, R. W. Propylthiouracil in treatment of hyperthyroidism. *Am. J. M. Sc.* 214: 545-552, 1947.
2. Bartels, E. C. Agranulocytosis during propylthiouracil therapy. *Am. J. Med.* 5:48-52, 1948.
3. Large, A., and Taylor, N. Treatment of patient with hyperthyroidism. *Am. J. M. Sc.* 220:213-224, 1950.
4. Beebe, R. T., Propp, S., McClintock, J. C., and Versaci, A. Fatal agranulocytosis during treatment of toxic goiter with propylthiouracil. *Ann. Int. Med.* 34:1035-1040, 1951.
5. Livingston, H. J., and Livingston, S. F. Agranulocytosis and hepatocellular jaundice: toxic reactions following propylthiouracil therapy. *J. A. M. A.* 128:422-425, 1947.
6. Julian, B., and Harris, T. L. Fatal agranulocytosis occurring during propylthiouracil therapy: report of case. *J. A. M. A.* 139:646, 1949.
7. Colwell, A. R., Jr., Sando, D. E., and Lang, S. J. Propylthiouracil-induced agranulocytosis, toxic hepatitis, and death: report of case. *J. A. M. A.* 148:639-641, 1952.
8. Lucké, B., and Mallory, T. Fulminant form of epidemic hepatitis. *Am. J. Path.* 22:867-945, 1946.
9. Lord, J. W., Jr., and Andrus, W. DeW. Changes in liver associated with hyperthyroidism: with study of plasma prothrombin levels in immediate postoperative period. *Arch. Surg.* 42:643-660, 1941.
10. McIver, M. A. Liver changes in hyperthyroidism. *Surgery* 12:654-669, 1942.
11. Moon, V. H. Pathology of secondary shock. *Am. J. Path.* 24:235-273, 1948.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39461

PRESENTATION OF CASE

First admission. A twenty-year-old nulliparous housewife entered the hospital because of abdominal pain.

The patient was perfectly well until the morning before admission, when she was seized with pain in the lower abdomen that subsided in the afternoon but recurred in the evening and persisted with varying intensity up to the time of admission. In addition she experienced intermittent pain in the right upper quadrant that bothered her when she walked or moved in bed. There was no nausea or vomiting, but she was anorectic and had two bowel movements on the day before admission. There was no urinary difficulty. She had had some vaginal discharge for a few days and slight bleeding during the day before admission. The last menstrual period had occurred about twenty-eight days before entry. The menses had started at the age of eleven, occurring regularly about every twenty-eight days and lasting four or five days.

Physical examination revealed a normal heart and clear lungs. The abdomen was soft and was tender in the right upper quadrant. Pelvic examination showed a small, firm cervix, movement of which caused exquisite tenderness. There was tenderness in both vaults, worse on the left side, with some thickening behind the cervix. Blood was present in the vagina.

The temperature was 99°F., the pulse 72, and the respirations 20. The blood pressure was 100 systolic, 70 diastolic.

The urine was normal. The blood hemoglobin was 14 gm. per 100 cc., and the white-cell count 15,100, with 80 per cent neutrophils. An Aschheim–Zondek test was positive.

The patient improved gradually. On examination two days later the uterus was normal in size and shape. Behind the uterus there was a 6-cm. mass, which was tense, cystic and slightly tender. The abdominal pain and tenderness and vaginal bleeding stopped in four days, and she was discharged on the seventh day.

Second admission (four days later). Two days after discharge, the patient began to have vaginal spotting again and on the following day used four pads even though on bed rest. This continued, but there was no abdominal pain.

Physical examination was negative. The size of the uterus was believed to be consistent with a pregnancy of about six weeks' duration. The temperature was 99°F., the pulse 88, and the respirations 20; the blood pressure was 100 systolic, 70 diastolic.

The urine was normal. The hemoglobin was 15 gm. per 100 cc., and the white-cell count 10,000, with a normal differential. The bleeding time was 4 minutes, and the prothrombin time 12 seconds (normal, 13 seconds). An x-ray film of the chest was normal.

The symptoms subsided for forty-eight hours after which she had three episodes of watery bowel movements, and in the evening began to have pain in the lower abdomen. This became more severe in the right lower quadrant and was associated with tenderness and rebound tenderness; later, the right-lower-quadrant pain was also associated with spasm and decrease of peristalsis. On pelvic examination, the cervix was tender on motion, and the right vault was tender and questionably full. The pain gradually subsided, recurring after about an hour. During the second episode, the hemoglobin was found to be 12.5 gm. per 100 cc. and the white-cell count 12,300; the temperature was 99.8°F. Pelvic examination the next morning revealed marked tenderness on both sides and a definite fullness on the right.

An operation was then performed.

Differential Diagnosis

Dr. Marshall K. Bartlett*: In summary this nulliparous woman of twenty was staining by vagina at the time that her period was due, had symptoms and signs of some acute process in the lower abdomen and had a positive Aschheim–Zondek test. I think I can safely assume that she was pregnant; the Aschheim–Zondek test is so accurate that the only reasonable assumption is that this woman was in an early phase of pregnancy. Was the complication something that was related to the pregnancy, or was it unrelated, merely happening to occur in a woman who was pregnant?

The commonest acute surgical complication involving the abdominal viscera that one sees with pregnancy is appendicitis. In this patient there were a great many things against that. In the first place the pain started in the lower abdomen. There was, to be sure, intermittent pain in the right upper quadrant, which does not help me much one way or the other. But from then on the signs on examination seem to have pointed to something in the pelvis. She had exquisite tenderness on movement of the cervix on the initial examination and, forty-eight hours later, a definite mass behind the cervix. I doubt if appendicitis would have behaved in that manner. She had minimal gastrointestinal symptoms and no nausea or vomiting, which is again more in favor of a lesion in the pelvis rather than appendicitis.

To consider other things that are unrelated to pregnancy, could this have been pelvic inflammatory disease? As we all know, that is an unusual complication of early pregnancy. There was no substantial elevation of temperature at any time and no chills, and the process subsided rather promptly during the first admission. It seems unlikely that that picture represented pelvic inflammatory disease from infection in the tubes.

Could this have been an ovarian cyst? An ovarian cyst is a relatively common cause of acute abdominal emergencies in pregnancy, but it fails to explain certain things in this history. The pelvic findings were variable: at first there was a thickening behind the cervix and then a mass behind the cervix; both were more on the left in the first admission; there were findings on the right, and no definite mass on the second admission. I should consider an ovarian cyst more seriously if the mass had been more definite and more consistent. If there was an ovarian cyst, there must have been some interference with its blood supply or hemorrhage into it to account for the acute symptoms. That would not account for the vaginal bleeding. A patient in early pregnancy with a twisted cyst does not have any particular reason for staining by vagina. I think the fall in hemoglobin from 15 to 12.5 gm. in the course of the forty-eight hours should not be overlooked; if that can be interpreted as I am planning to interpret it, I have to assume that she had lost a certain amount of blood, presumably into the peritoneal cavity. An ovarian cyst would not account for the blood loss.

Could endometriosis have caused this kind of picture? Endometrial cysts that rupture are seen occasionally during pregnancy. Even though endometriosis and pregnancy are not supposed to be particularly compatible one occasionally sees trouble from an endometrioma during pregnancy. Again, I do not see how that could account for the vaginal staining and the fall in the hemoglobin, which I think must have represented a fair amount of blood loss.

Among the conditions that are related to pregnancy, which ones could explain this picture? As we all know, bleeding from the corpus hemorrhagicum or corpus luteum may occur at any time from ovulation up to the onset of menstruation, although it is most frequent at the time of ovulation. As a matter of fact it occasionally occurs a day or two after the period has started. As far as I know, only twice have we seen bleeding from the corpus luteum of pregnancy. We had 2 patients,

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each about six weeks pregnant, in the Emergency Ward, in rapid succession, who had what we thought were ectopic pregnancies. Both proved to have hemorrhage from the corpus luteum of pregnancy. That was new to me and it does not happen very often. This patient had not skipped a period; her period was due, and she was staining. At that stage I think she could have bled from the corpus luteum, but again that would not account for the vaginal staining, which began before the abdominal pain began.

It seems that an ectopic pregnancy explains the symptoms and signs that we are given here more fully than anything else. To be sure, it was a little early for vaginal bleeding from an ectopic pregnancy. Typically such patients are perhaps two weeks past their expected period before they begin to stain, but that does not necessarily rule it out. The Aschheim–Zondek test does not tell us whether the pregnancy is within the uterus or ectopic; it means only that there is a living ovum in contact with the maternal circulation and so does not rule out an ectopic pregnancy. It seems to me that a tubal pregnancy could bleed enough to cause the initial episode, which quieted down in the hospital on bed rest, with cessation of the abdominal pain and the vaginal staining. When the patient returned home the staining started again; she therefore came back into the hospital. After she had been in the hospital about forty-eight hours, she began to have abdominal pain, which was more severe and was associated with more tenderness, with spasm and with decreased peristalsis, and had a fairly substantial fall in the hemoglobin, acute tenderness on movement of the cervix and fullness in the vault. I think that an ectopic pregnancy explains those findings better than any other condition that I have considered.

Clinical Diagnosis

Ruptured tubal pregnancy.

Dr. Marshall K. Bartlett's Diagnosis

Ruptured tubal pregnancy.

Anatomical Diagnosis

Ruptured tubal pregnancy.

Pathological Discussion

Dr. Benjamin Castleman: Dr. Ingersoll, will you tell us the clinical impressions and the reason that the operation was delayed?

Dr. Francis M. Ingersoll: I think that should be explained. This young woman was the bride of one of the residents, who met me in the corridor one noontime and took me home to see her. At that time the right-upper-quadrant pain was the major complaint. She had exquisite tenderness in the pelvis. Then we did not have the positive Aschheim–Zondek test or any of the facts that Dr. Bartlett was given. We were, I think, overimpressed by the complaints in the upper abdomen and were also influenced by the strong desire of the husband that no surgical intervention be carried out unless there was an absolute indication for it, so we elected to follow this patient. As the differential diagnosis that Dr. Bartlett has gone through reveals, she had an ectopic pregnancy that we were "sitting on." We had consultations with various physicians, all of whom entertained that diagnosis, but waited to operate until she bled internally and had excruciating pain and surgery was imperative.

At operation, it was not an unusual ectopic pregnancy; there was about 500 cc. of blood in the abdominal cavity. A partial salpingectomy was readily performed.

Dr. Castleman: The specimen that Dr. Ingersoll removed included the terminal two thirds of the tube; he was able to leave the proximal third of the tube attached to the uterus. At the site where the rupture occurred some of the placental tissue protruded from the markedly distended tube, which was filled with blood.

Dr. Ingersoll: I should like to say that the difficulty the surgeon has in handling other physicians' wives is that no matter how hard he tries not to treat them differently, the fact that it is another physician's wife does enter into his mind and he is not so quick to operate as he is on other patients.

CASE 39462

Presentation of Case

A seventy-five-year-old retired sign painter was admitted to the hospital with a chief complaint of weakness.

Because of memory defect and debilitation the history was vague. Some of the information was obtained from the patient's daughter, with whom he lived. He had apparently been well until about six months before admission. He stated that he had been seen by his local physician shortly before and had been told that "his blood was fine." Then he began having "indigestion" associated with flatulence and occasional episodes of vomiting, but no abdominal pain. The vomitus allegedly contained small quantities of blood once or twice. He became progressively weaker. Throughout this period there were infrequent episodes of mild pain in the right upper quadrant and right lower part of the chest that were intensified by motion, deep respiration, swallowing and lying on the right side. He was admitted to another hospital, where studies revealed an anemia and a diaphragmatic hernia was demonstrable by x-ray examination. He received liver-extract injections daily for two weeks in the hospital and weekly for sixteen weeks after discharge. There was subjective improvement during this period, and petechiae, which had been noted over the legs and outer aspects of the ankles, disappeared. He was

doing fairly well at home except for slowly progressive weakness until two to three weeks before admission, when he had several severe epistaxes. There had been a total weight loss of 30 pounds. He had had mild exertional dyspnea for years and recent slight productive cough. He occasionally passed small amounts of bright-red blood in the stools. He had moderate urinary frequency and nocturia. He was referred to this hospital with a diagnosis of secondary anemia of unknown etiology.

The past history revealed an illness eight or nine years previously that was said to have been pneumonia with "cardiac complications." Eighteen years before admission there was sudden and permanent decrease in visual acuity in the right eye. Thirteen years later the patient experienced a similar, sudden visual loss involving the left eye. For this he was admitted to another hospital, where complete occlusion of the left superior temporal artery secondary to arteriosclerosis was noted. Right optic atrophy was present. In addition to these findings the heart border was percussed 11.0 cm. to the left of the midsternal line. There was a Grade 2 apical systolic murmur and a Grade 1 aortic systolic murmur, normal sinus rhythm and blood pressure of 125 systolic, 75 diastolic. Two urinalyses were negative except for specific gravities of 1.006 and 1.010. Blood studies were normal.

Physical examination on entry revealed an elderly, nearly blind man who was drowsy, had a wandering gaze and was tachypneic. The skin was pale and sallow although the lips were pink. A few tiny petechiae were present over the chest anteriorly. Several slightly enlarged, firm lymph nodes were palpable in the axillas and groins. The eyes displayed optic atrophy and bilateral lenticular opacities with vision limited to finger perception only. A few petechiae were present over the palpebral conjunctivas. Both fresh and old blood was present in the left nares. Dried blood was present over the fauces and palate. The lungs were clear. The apical beat was palpable 9.0 cm. to the left of the midsternal line in the fifth intercostal space. A loud, decrescendo, Grade 3, systolic murmur, widely transmitted into the neck and to the apex, was heard in the left third intercostal space. The abdomen was soft, and the liver edge was felt 3 fingerbreadths below the costal margin and was smooth and nontender. The spleen was palpable 2 fingerbreadths below the costal margin. Rectal examination was negative. Neurologic examination was not remarkable except for the drowsiness.

The temperature was 101°F., the pulse 86, and the respirations 38. The blood pressure was 130 systolic, 60 diastolic.

Urinalysis revealed an acid reaction and a +++ test for albumin; the sediment contained 3 to 5 coarse granular and 0 to 1 fine granular casts, 3 to 4 white cells and 90 to 100 red cells per high-power field. Examination of the blood disclosed a hemoglobin of 5.0 gm., a red-cell count of 3,100,000 an MCV (mean corpuscular volume) of 71 cubic microns (normal, 80 to 94), an MCH (mean corpuscular hemoglobin) of 17 micromicrogm. (normal, 27 to 32), an MCHC (mean corpuscular hemoglobin concentration) of 23 per cent (normal, 33 to 38) and a white-cell count of 6000, with 80 per cent mature neutrophils. The hematocrit was 22 per cent, the platelet count 240,000 and the reticulocyte count 5 per cent. The serum protein was 6.2 gm., the albumin 2.4 gm., the globulin 3.8 gm., the nonprotein nitrogen 235 mg., the serum bilirubin 0.5 mg. total, and the alkaline phosphatase 11.8 units per 100 cc. A stool was guaiac positive. A Coombs test was negative. A sternal-marrow examination showed normal cellularity with a myeloerythrocyte ratio of 8:1, with the myeloid elements displaying a slight shift to the left. Megakaryocytes were plentiful. The cephalin flocculation was ++++ in twenty-four and forty-eight hours. The prothrombin time was 16 seconds (normal, 14 seconds). An electrocardiogram showed a QT interval of 0.40 second but was otherwise normal. A roentgenogram of the chest disclosed enlargement of the left ventricle and bilateral engorgement of the pulmonary vessels.

The clinical course was progressively downhill despite transfusions and supportive measures. Weakness and mental depression became more pronounced. A few scattered petechiae having a tendency to fade and recur were noted over the anterior part of the chest and pressure points of the extremities. The nonprotein nitrogen gradually rose, reaching a level of 285 mg. per 100 cc. on the eighth hospital day. Between the third and tenth days the sodium, potassium and chloride increased from 135 to 152, 6.1 to 7.4 and 113 to 124 milliequiv. per liter respectively. The carbon dioxide was 13.0 milliequiv. per liter on the third day and 11.0 on the tenth day. Phosphorus and calcium were 6.1 and 9.1 mg. per 100 cc. respectively on the eighth day. The blood hemoglobin was 8.0 gm. per 100 cc. on the tenth day; a second white-cell count was 11,000. Repeat guaiac tests of the stool were + to ++++. Cystoscopic examination on the third day revealed no urinary-tract obstruction. Some edema about the right ureteral orifice was described, but clear urine was obtained through ureteral catheters. A Foley catheter was left in the bladder after cystoscopy. The daily urinary output ranged between 200 and 1750 cc. thereafter, with an average of 1000 cc. A repeat urinalysis on the tenth hospital day showed the same findings as before. The specific gravity was not recorded. On the eleventh hospital day, after having been profoundly lethargic with deep labored respiration for five to seven days, the patient had a generalized convulsion, which began in both arms, involved the legs about 30 seconds later and was finally associated

with twitching of the facial musculature on the left. He was found dead shortly afterward.

Differential Diagnosis

Dr. Frederic B. Mayo*: This seventy-five-year-old man had a subacute illness with widespread manifestations of disease involving the skin and pulmonary, cardiovascular, gastrointestinal, renal and hemopoietic systems. Was this a diffuse disease, such as a collagen disease, leukemia or multiple myeloma, or was it localized in one organ with secondary manifestations in the other systems? It might be worth while to speak first about the renal disease since that seemed to be the major difficulty and it finally killed him. The uremia alone, I believe, could have caused nearly all the signs and symptoms, except those of liver disease. It would be interesting to know what the urine showed and what the nonprotein nitrogen level was when he was admitted to the other hospital for the gastrointestinal series six months before this admission. If he was uremic at that time, one might say that this was a case of progressive renal disease terminating in uremia.

He had severe arteriosclerosis, as evidenced by retinal-artery thromboses eighteen and five years before admission. Could he have had nephrosclerosis? A point against that is the fact that the blood pressure was recorded as normal five years before admission and again on admission although conceivably the degree of anemia present could have reduced the hypertension. There is no way of ruling glomerulonephritis in or out at the present moment.

He obviously had hepatic disease in addition to the renal disease. Was this cirrhosis of the liver, as a second condition, or was it liver disease related to the kidney disease? We know that toxins, such as the hydrocarbons, will produce liver and renal disease. There was no history of such an exposure, and the course was too long. Could he have had polycystic disease of the kidney and liver? Weil's disease involves both systems, but there is no evidence for that. Sarcoidosis is a possibility, but it rarely results in functional disturbance.

The hepatorenal syndrome, although it is poorly understood and constitutes a catchall, should be mentioned. Patients who have this syndrome die with a high fever, usually with jaundice and with much more evidence of liver disease than this patient had. The nonprotein nitrogen in the so-called hepatorenal syndrome rarely goes above 100 mg. per 100 cc. So far we have no diagnosis. May I see the x-ray films?

Dr. Stanley M. Wyman: These two films of the chest show the lung fields to be somewhat more engorged than usual. Because the film was taken with the patient lying on his back, part of the apparent change in size of the vessels and the apparent enlargement of the left-ventricle portion of the heart shadow are due to magnification. The aorta is not remarkable. There is a small amount of calcification in its arch.

Dr. Mayo: Can you see calcification in the valves?

Dr. Wyman: I cannot, but in this film, which is quite lightly penetrated, calcification that should lie over the spine might well be overlooked. I do not identify any localized disease with certainty. There is a suggestion of a small density in the upper pole of the left hilus that is not sufficiently certain for me to name it; the soft tissues of the back could be folded over to form that shadow. I am not happy about calling the lungs completely clear, but I cannot quite make them out as abnormal.

Dr. Mayo: Do you see any evidence of pulmonary infarction?

Dr. Wyman: No.

Dr. Mayo: Can you tell me anything about the liver size?

Dr. Wyman: No.

Dr. Farahe Maloof: Is the mediastinal shadow wide?

Dr. Wyman: I thought that was due to prominent vessels. Were you thinking of a substernal soft-tissue mass such as an enlarged thyroid gland? This degree of prominence of the vessels is sometimes noted in the superior mediastinum as well as in the hilar region in films taken with the patient in the supine position.

Dr. Mayo: The patient had petechiae, irritation of the right leaf of the diaphragm, a large spleen and hematuria — findings that add up to embolic phenomenon and suggest the diagnosis of subacute bacterial endocarditis. The threshold of suspicion of subacute bacterial endocarditis has become so low that the recent literature[1] stresses the fact that anybody admitted to the hospital with unexplained anemia should be suspected of that disease. This

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man had not only the anemia but also a cardiac murmur, fever, emboli, nosebleeds, weakness, weight loss and vague gastrointestinal symptoms, all of which are compatible with subacute bacterial endocarditis. Was the blood cultured?

DR. WINFIELD S. MORGAN: No.

DR. MAYO: In different series reported in the literature[2] the incidence of people with subacute bacterial endocarditis who died in uremia varied for 0 to 20 per cent. In another series of patients over the age of forty-five,[3] the males outnumbered the females 4:1. In this series almost 50 per cent of the patients had aortic-valve disease. There are two points against subacute bacterial endocarditis, one of which is the murmur. If a man of this age had severe subacute bacterial endocarditis of six months' duration on an aortic valve, he should have had some valve changes that should have been heard as a diastolic murmur. Would you agree with this, Dr. Bland?

DR. EDWARD F. BLAND: In general, yes; but it is not invariably so.

DR. MAYO: The other point, a major one, is the liver disease. Can the liver disease be explained by subacute bacterial endocarditis? The literature gives me some support if I assume there were emboli and infarction of the liver. Pass,[4] in 1935, reported 52 cases of infarction of the liver, in 13 of which there were multiple emboli as a result of subacute endocarditis and in 22 of which there was thrombosis due to periarteritis nodosa. I looked through the literature for evidence of impaired liver function after infarcts in the liver and could find none. Is it in the realm of possibility that multiple infarcts of the liver could produce abnormal liver-function tests without causing jaundice?

DR. DANIEL S. ELLIS: It is quite possible to have extensive infarction in the liver without jaundice.

DR. MAYO: Another diagnosis that is possible, but I do not think can be proved or disproved, is polyarteritis nodosa, which is often thrown into the picture to await the pathologist's diagnosis. Was a biopsy done in this case?

DR. MORGAN: No.

DR. MAYO: I cannot make a definite diagnosis, and I am not sure that the proof of the pudding is in the clinical protocol. I shall close with the diagnosis of subacute bacterial endocarditis, superimposed on an arteriosclerotic aortic valve, with multiple emboli to the spleen, kidneys and, I hope, the liver.

DR. BERNARD M. JACOBSON: How do you explain the long-standing hypochromic anemia with evidence of continued blood loss from the gastrointestinal tract at the time he was in the hospital?

DR. MAYO: I do not know how long the hypochromic anemia had lasted. Six months before admission, shortly before he became sick, the blood was said to be all right.

DR. JACOBSON: What evidence of liver disease did this man have?

DR. MAYO: He had a large liver on palpation. He also had a high alkaline phosphatase, a reversed albumin-globulin ratio and a ++++ cephalin-flocculation test.

DR. JACOBSON: It is not unusual to see a ++++ cephalin-flocculation test with severe chronic anemia?

DR. ELLIS: You do not explain a cephalin flocculation of ++++ or an albumin level of 2.5 gm. and a globulin of 3.8 gm. on the basis of anemia alone?

DR. JACOBSON: It does occur in a long-standing chronic anemia, such as pernicious anemia; the high serum globulin may have been due to endocarditis.

DR. ELLIS: I think the evidence for liver disease is ample. I suspect that this patient had some parenchymal liver disease peculiar to the liver itself and not secondary to the systemic disease elsewhere.

DR. MORGAN: Dr. Bland, what do you think this patient had?

DR. BLAND: I think he had a subacute bacterial endocarditis. Elderly people often fool us with that disease because they may have little or no fever, they are debilitated and anemic, and they die in uremia. The course is so unlike that of this illness in younger people that we sometimes do not think of this possibility.

DR. MAYO: With a second diagnosis of cirrhosis of the liver?

DR. BLAND: No; only subacute bacterial endocarditis.

DR. ELLIS: I am willing to accept the possibility that he had a subacute bacterial infection, but I think he also had primary liver disease.

CLINICAL DIAGNOSES

Chronic pyelonephritis, with uremia.
Portal cirrhosis of liver.
Secondary anemia.

DR. FREDERIC B. MAYO'S DIAGNOSES

Subacute bacterial endocarditis on arteriosclerotic aortic valve.
Multiple emboli to spleen, liver and kidneys.

Anatomical Diagnoses

Subacute bacterial endocarditis (Streptococcus viridans), *mitral valve.*

Glomerulonephritis, endocarditic type, focal and diffuse, severe, with uremia.

Splenomegaly (weight 570 gm.).

Adenocarcinoma, sigmoid.

Pulmonary congestion and edema.

Bronchopneumonia.

Diffuse colloid goiter.

Pathological Discussion

Dr. Morgan: At autopsy the lungs were moderately heavy, weighing about 1350 gm., and exhibited considerable congestion and edema. In addition there was bronchopneumonia in both lower lobes. The heart was moderately enlarged, weighing 470 gm., and the coronary arteries were severely narrowed although no occlusions could be demonstrated. There were many petechiae over the epicardial surface, and all chambers of the heart were moderately dilated, especially the left ventricle. The chordae tendineae and the valves were all normal in appearance except for slight thickening of the posterior leaflet of the mitral valve, where there was an adherent, reddish vegetation measuring about 2 by 1.5 by 0.8 cm.

Culture of the vegetation grew out *Streptococcus viridans*, and microscopical sections demonstrated numerous clumps of bacteria, portions of which were calcified, enmeshed in the fibrin and fibrous stroma, with no leukocytic infiltration. In view of the absence of any clear-cut evidence of old endocarditis — the slight thickening of the posterior leaflet being attributed to the present infection — it seems as though we are dealing with the unusual development of subacute bacterial endocarditis on a previously normal valve.

As was expected, the kidneys were the second site of disease although their weight was normal, and grossly they were not remarkable except for scattered petechiae. Microscopically, they revealed a diffuse, severe glomerulitis of the type seen in association with subacute bacterial endocarditis, characterized by focal fibrinoid necrosis of one or more capillaries of the glomerular tuft or in some instances of the whole glomerulus. In this case the lesions ranged from recent ones to those in which there was partial or complete healing with fibrous replacement. The tubules contained red blood cells and hemoglobin casts, undoubtedly the result of damage to the glomeruli.

Current opinion about the etiology of glomerular lesions of this sort[5] is against the traditional belief that they are due to showers of emboli swept off from a vegetation, and suggests a hypersensitivity state as a more likely explanation. Although there is no conclusive evidence for this concept, it is supported by the fact that few of the glomeruli show bacteria and, in cases of acute bacterial endocarditis in which the vegetations are equally friable, this type of lesion is practically never seen. As Dr. Mayo said, about 50 per cent of patients with subacute bacterial endocarditis have glomerulitis of this type; however, relatively few, about 8 per cent, go on to die in renal failure.

Dr. Bland: Can you tell from either the kidneys or the calcified valve how long this disease had been going on?

Dr. Morgan: All I can say is that it was consistent with the six-month period of illness.

There was no other significant renal disease so we attributed the renal failure to the glomerulitis. The liver was normal, grossly and microscopically. The spleen was enlarged, weighing 600 gm., and showed toxic changes. The previous urinary symptoms could be explained on a basis of benign prostatic hypertrophy, and an incidental finding was an adenocarcinoma of the sigmoid, which may have accounted for the blood on the stool. Finally, I think I should mention for Dr. Maloof's benefit that there was a nodular goiter weighing 55 gm.

References

1. Parsons, W. B., Jr., Cooper, T., and Scheifley, C. H. Occult subacute bacterial endocarditis manifested by hematologic abnormalities, including pancytopenia. *Ann. Int. Med.* 39:318-325, 1953. Anemia in bacterial endocarditis. *J. A. M. A.* 153:14-16, 1953.
2. Villa real, H., and Sokoloff, L. Occurrence of renal insufficiency in subacute endocarditis. *Am. J. M. Sc.* 220:675-661, 1950.
3. Traut, E. F., Carter, J. B., Gumbiner, S. H., and Hench, R. N. Bacterial endocarditi in elderly. *Geriatrics* 4:205-210, 1949.
4. Pass, I. J. Infarction of liver. *Am. J. Path.* 11:503-526, 1935.
5. Allen, A. C. *The Kidney: Medical and surgical diseases.* 583 pp. New York: Grune & Stratton, 1951. P. 168.

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WMA MEETS AGAIN

THE World Medical Association, a brief and incomplete account of whose Seventh General Assembly is presented elsewhere in this issue of the *Journal*, continues to add new member associations to its roster and to meet successfully the disintegrating forces always present in such organizations. These are the natural consequences of different tongues and dissimilar customs, of various cultural cleavages, of fixed habits of nationalistic thinking with the jealousies and national ambitions that cannot fail to be present, and of the distances that must be traveled, especially by a small number of delegates who are penalized by being far removed from those centers where meetings are most likely to be held. For it is a matter of some concern to the delegates from South Africa, Australia, India, Japan, South Korea, Pakistan, the Philippine Islands and Thailand, and now Indonesia, that six of the Assemblies so far held have been in London, Paris, Geneva, Stockholm, Athens and The Hague.

There are also integrating forces, which include the desperate need for all such co-operative international organizations as can be maintained, and the will of a determined group of physicians of various countries, languages and cultural backgrounds that this one shall succeed.

In this particular Assembly too much concern seemed to be expressed over the rights and rewards of the physician himself to allow any very high plane of discussion to be established in the first session or two. Necessary as it is that views should be exchanged on the social and economic problems of practitioners in the various countries represented, such discussions should be subordinated to those related to advances in the technics of developing and distributing medical care more and more widely and increasingly effectively. That these socially and scientifically constructive matters are not neglected is evidenced by the work of the Association that continually goes forward in the fields of medical education and medical care and on the international pharmacopoeia and medical ethics, and by the suggestion that the Association should take over from the United Nations Educational, Social and Cultural Organization the publication of the long-needed volume on medical documentation and the standardization of medical abbreviations. As Dr. Clegg intimated in discussing this point, bureaucracy, precious as it is, should be kept in its proper place.

What the World Medical Association appears to need more than anything else in order to have wheels put under it is such a persistent program of publicity that its name, its plans and its progress will be known to all physicians. After seven years there should be no further excuse for confusing WMA with WHO, and a knowledge of the growth and accomplishments that have taken place during these years should assure the financial support that is necessary if the Association is to continue its work of promoting international understanding among physicians.

HOP DERMATITIS IN HEREFORDSHIRE

THE use of hops to impart a better flavor to malt liquors apparently antedates the art of printing and hence the medical literature, but there is little reason to doubt that the brown October ale that turned the head of Friar Tuck and addled the pate of Little John[1] was not flavored with the cones of *Humulus lupulus*. Unfortunately, in Pyle's[1] study of early Nottingham, so much time is devoted to a description of anthropologic events that the occupational diseases of early hop pickers are slighted. However, hop pickers' dermatitis has been accorded serious study of recent months by Cookson and Lawton.[2]

Apparently, hops were regarded as noxious, and their use was forbidden by the Hereford (England) City Regulations of 1557. "And that no bruer shall sett Anye hoppes or asshes in theire Ale upon peyne of XX[s] for evy defalte." Despite this ordinance the apprehension was recorded in 1513 of "Wyllm Collyer for bere Hoppis in ye ale, Alson Coke for bere hoppis in hyr ale." It is not stated whether Collyer and Coke had dermatitis. Cookson and Lawton[2] assume, however, that Hereford citizens included hop pickers at least as early as the sixteenth century, and it seems reasonable to infer that not a few of them itched.

Today, at any rate, "hop rash" is well known to the pickers; it is a form of contact dermatitis 22 cases of which are reported to have begun with picking on September 4 and continuing until the end of picking on October 4, 1952. No less than 11 of these patients were forced to give up their employment, an indication of the discomfort of the disease since hop picking is "a pleasant and lucrative occupation." One healthy male busheler started work on September 4, "having never previously seen a hop." He made the beginner's mistake of plunging his right arm into the picker's crib and helped the hops into the measure with the left hand. One can hardly wonder that, after eight full days of busheling, an irritable papular eruption on the back of the hands and the flexor surface of the forearms developed, corresponding fairly accurately to the site of staining from the hop juices. He even had a slight erythema round his eyes and at the side of his nose, and a patch test to hop-cone was strongly positive.

After appropriate patch testing, Cookson and Lawton[2] concluded that dermatitis may in some cases be due to fresh hop oil and that it was seldom if ever due to hop dogs (caterpillars) or hop fleas, which usually bite the legs of pickers and are readily distinguishable by experienced workmen. No practical program for control was developed, nor was any consideration given to the possibility that the usual mechanism of desensitization is by the physiologic consumption of hop oil in malt liquors. However, the idea seems worth pursuing in the light of the low incidence of clinically manifest disease — about 1 case for each 300 hop-pickers.

REFERENCES

1. Pyle, H. *The Merry Adventures of Robin Hood.* 316 pp. New York: Charles Scribner's Sons, 1929.
2. Cookson, J. S., and Lawton, A. Hop dermatitis in Herefordshire. *Brit. M. J.* 2:376-379, 1953.

EDWIN J. COHN

EDWIN J. COHN, who never studied medicine and almost never saw a patient undergoing treatment, exerted an influence on the progress of medicine matched by few contemporary men. He began his scientific work under the influence of Lawrence J. Henderson, studying the chemistry of sea water to learn its significance for the living organism, and examining the physiology of spermatozoa under F. R. Lillie in Chicago. Soon he acquired the conviction that the investigation of proteins was the foremost current problem of biology, and from that time forth he devoted himself to the study of proteins with unflagging zeal. After working with two great masters in the field, T. B. Osborne in New Haven and S. P. L. Sörensen in Copenhagen, he returned to Harvard in 1920 and worked there until his death on October 1, 1953.

For the first twenty years of this period, his studies were primarily devoted to fundamental investigations of the physical chemistry of proteins, amino acids and peptides. Characteristically, he became the center of a group of investigators, some in his own and some in other laboratories, and inspired scientists of very diverse talents to join with him in the attack on these fundamental problems. In 1926 the discovery of the liver treatment of pernicious anemia by Minot and Murphy turned him temporarily aside from these researches and

led him for the first time to attack a problem of direct clinical importance — the separation from whole liver of the factor active in pernicious anemia. From the practical point of view the results were in many respects brilliant: — the concentrated liver extracts prepared by Cohn's methods rapidly replaced whole liver in the treatment of the disease. However, to him the achievement was far from satisfying; the isolation of the active principle in pure form still eluded him, and the very effectiveness of the treatment practically eliminated the only laboratory animal then available for the tests of the purified fractions — namely, the human patient suffering from the active disease. Indeed, the isolation of the active principle came later only after the development of a bacterial growth method of assay for the active principle. Shortly after 1930, Dr. Cohn turned away from this problem, which had given him the experience in working with clinicians that was to prove invaluable ten years later, and returned to an intensive study of the physical chemistry of amino acids and peptides. He envisaged these small molecules of known structure as simple models and prototypes to serve as a basis for the understanding of the reactions and properties of the proteins, with all the baffling complexity of their structural pattern. With a group of enthusiastic associates, at Harvard and M.I.T., he worked out a pattern of well defined principles that served to elucidate the relations between solubility and structure, and the significance of the powerful electrical interactions determining them. Not a few chemists and others recognized the fundamental scientific significance of the work, but scarcely anyone could have foreseen that it would prove an indispensable foundation for the later development of fractionation procedures that were to revolutionize the uses of products derived from blood. Seldom has the transition been so rapid, within a single laboratory, from the study of very abstract problems of no apparent contemporary practical significance to work of the most urgent practical importance in a time of great crisis. Yet the continuity in the thinking of the workers in the laboratory was essentially unbroken.

The development of the plasma fractionation program during World War II is a story that has often been told, but the magnitude of the vision that inspired Edwin Cohn, then and later, has perhaps not been fully appreciated. The wartime emergency called fully into play his powers as a great leader and organizer, who drew together chemists, clinicians, pathologists, immunologists and others to achieve the separation and purification of serum albumin, gamma globulin, fibrinogen, thrombin and other fractions of human plasma, and their application to clinical use after a program of careful preliminary testing. Dr. Cohn, however, was never satisfied with the immediate achievement of a practical goal. He envisaged a fractionation program that was to become even more complete in the separation of the innumerable protein components of plasma, each to be devoted to its particular use, and the separation of the formed elements of blood, as well as the plasma proteins, by means so gentle as to preserve them as nearly as possible in their state in nature. The wartime fractionation processes were replaced by newer methods involving precipitation by metallic ions such as zinc, which could then be removed by ion-exchange resins; a newly developed machine of extraordinarily ingenious design made many of the procedures automatic. The consequences may be far reaching for the whole national blood program, for the public health and for national defense, in ways that cannot yet be fully anticipated. The passing of this extraordinary man is recorded with deep regret.

"HOME IS THE HUNTER"?

The southward advance of the annual hunting season, now at its crest, reminds one that the peacetime sailor has no less a chance of returning from the sea than has the hunter of finding himself safely home from the hill.

The warning is justified by the researches of the Metropolitan Life Insurance Company's staff of statisticians, who have found that firearm accidents currently take about 2200 lives annually in the United States. The three major risks in hunting, according to this report, are walking into the line of fire, the accidental discharge of loaded

weapons carelessly carried, and the mistaking of hunters for the quarry.

In the last category, representing the greatest degree of criminal negligence, more hunters are killed by members of their own party than by strangers. Eighty per cent of the cases of sylvan manslaughter, in fact, are those of sportsmen thus slain by their friends.

The hunter who fires before he knows exactly what he is aiming at is always culpable, although it must be acknowledged that sometimes the idiocy of the victim is a contributing factor. Only common sense and the lack of a pair of antlers in the line of vision stayed the trigger finger of one hunter, who came upon a resident of New York City creeping through the New England jungle in a fur coat.

The home, as usual, remains the proper place in which to die — although in these familiar surroundings more firearm fatalities occur than in field and forest combined.

From the accounts of correspondents, it seems there is something of a falling off in the classes at various schools the present season... If these reports are true, it is not perhaps a matter of regret...where the competition is urgent, the qualifications are apt to be below a proper standard.

Boston M. & S. J. *November 16, 1853*

MASSACHUSETTS MEDICAL SOCIETY

SECRETARY'S NOTE

A copy of the *Circular of Advance Information for Councilors*, containing committee reports and other matters to be acted on at the February meeting of the Council, will be sent to any fellow on request to the Secretary, 22 Fenway, Boston, before December 4.

ROBERT W. BUCK, M.D., *Secretary*

COMMITTEE ON MATERNAL WELFARE

The Committee on Maternal Welfare is redoubling its efforts to study and analyze all maternal deaths in the State, and will begin a new five-year program in 1954. All physicians are, therefore, urgently requested to inform the Committee by telephone *immediately* of any maternal death.

In the western part of the State, this call should be made to Dr. Arthur F. G. Edgelow, 76 Maple Street, Springfield (telephone, Springfield 4-5926).

In the eastern section of the State the call should go to the chairman, Dr. John F. Jewett, 319 Longwood Avenue, Boston (telephone, BEacon 2-3911), or to Dr. Benjamin F. Cornwall, of Salem, Dr. Joel M. Melick, of Worcester, or Dr. Robert H. Goodwin, of New Bedford.

Autopsy information is of the greatest importance, and a post-mortem examination should be requested in every case. If a pathologist is not locally available, the Committee will supply this service *without charge* through the courtesy of Dr. William Ober, pathologist to the Boston Lying-in Hospital.

JOHN F. JEWETT, M.D., *Chairman*

BOOK REVIEWS

Ophthalmic Plastic Surgery. By Sidney A. Fox, M.S. (Ophth.), M.D. 8°, cloth, 290 pp., with 133 illustrations. New York: Grune and Stratton, 1952. $15.00.

This book, written for the practicing ophthalmologist, presents only the procedures that the author has used and found satisfactory. The first four chapters deal with the anatomy of the eyelids and eyebrows and the fundamentals of surgery applied to the correction of defects of these regions. The remaining chapters are devoted to the reporting of various defects of the eyebrows and the eyelids, with descriptions of the operative procedures. The book is clearly presented and well illustrated with pictures and diagrams. Each chapter is supplemented with a bibliography for additional references for those interested in a particular subject.

In a book of this type it is natural for a reviewer to find certain procedures that could have been omitted and others that could have been added, but, as the author points out, it is not an encyclopedia but a book based on his own experience, and it should be a valuable addition to the reference library of the ophthalmologist and plastic surgeon.

The volume is well bound and printed on paper of good quality.

V. H. KAZANJIAN, M.D.

Psychology of Physical Illness: Psychiatry applied to medicine, surgery and the specialties. Edited by Leopold Bellak, M.D. 8°, cloth, 243 pp. New York: Grune and Stratton, 1952. $5.50.

The art of psychiatry is ancient. It can be traced back to the Island of Cos, but the new science of psychiatry is only fifty years old, or at the most sixty, deriving largely from Western Europe. It is not old enough yet to have a "geriatrics" of its own; however, the science of psychiatry is maturing and spreading as all good branches of science do. This book documents in particular the application of general psychology to special types of physical illness. It puts forth the application of psychiatry to internal medicine, surgery and the specialties. It is carefully written, well organized and most ably presented. The case histories will be especially interesting to practicing physicians and internist surgeons, and each other specialist will find a chapter of particular interest to his specialty. The bibliographies given at the end of each chapter fill in the defects that resulted from condensation. This is a practical and useful book.

MERRILL MOORE, M.D.

Child Development: The process of growing up in society. By William E. Martin and Celia Burns Stedler. Under the editorship of Willard B. Spalding. 8°, cloth, 519 pp., with illustrations. New York: Harcourt, Brace and Company, 1953. $6.50.

The authors have carried over their educational experience and training into the production of a book that should prove excellent textbook material for the educational student interested in child development, particularly for purposes of teaching. This book is in language simple enough for parents to understand, and physicians will likewise enjoy reading it, although the language is definitely nontechnical for either the physician or the psychiatrist.

Successive chapters deal with the effects upon and the growth of the child within the society. The socialization process is explained, many of the socializing agents as a child grows and develops being described. The section on socialization from a psychoanalytic point of view is well written and factual and is organized so that an early student in the field can understand the psychodynamics involved in the child's development.

PIERCE D. NELSON, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Modern Practice of Obstetrics. By D. M. Stern, M.A., M.B., B.Ch. (Cantab.), F.R.C.S., F.R.C.O.G., obstetric and gynecologic surgeon, West Middlesex Hospital and its annexes, gynecologic surgeon, Staines Hospital, lecturer in obstetrics, West London Hospital Medical School, and examiner to the University of London, the Examining Board in England and the Central Midwives Board: and C. W. F. Burnett, M.D. (Lond.), F.R.C.S., F.R.C.O.G., obstetric and gynecologic surgeon, West Middlesex Hospital and its annexes, gynecologic surgeon, Staines Hospital, assistant lecturer in obstetrics, West London Hospital Medical School, and examiner to the Central Midwives Board and the General Nursing Council. 4°, cloth, 248 pp., with 139 illustrations. London: Bailliere, Tindall and Cox, 1952. $7.00. (Distributed by Williams and Wilkins, Baltimore.)

This British book, which is based on the experience gained from about 50,000 consecutive deliveries during the past sixteen years, described obstetrics as practiced at the West Middlesex Hospital. William Smellies' "Requisite qualifications of accoucheurs, midwives and nurses who attend lying-in women" (1752) is reproduced on the inside of the front cover. There is a good index, and the publishing is excellent.

The Low Sodium Cook Book: How to prepare tasteful meals for the low sodium or low salt diet—including suggestions for the low sodium, low fat, low cholesterol diet. By Alma S. Payne, M.A., and Dorothy Callahan, B.S., research dietitian, Massachusetts General Hospital. With an introduction by Francis L. Chamberlain, M.D., M.Sc.D., of the University of California Medical School. 12°, cloth, 477 pp. Boston: Little, Brown and Company, 1953. $4.00.

The authors have written a practical book for persons requiring special diets for hypertension and other conditions and diseases. The sodium content of over 900 items, as well as the latest information on usable commercial products, is given. Adaptations are given for low-fat and low-cholesterol diets. The material is presented in the form of recipes showing the sodium and fat content of every recipe and the calories. In addition there are chapters on the home freezer and how it may be utilized and on food for trips and on eating out. There is much useful information on classes of foods, and there are menus for special celebrations, such as Thanksgiving and Christmas dinners. The appendixes contain a mass of information in tabular form of the sodium, cholesterol and fat content of common foods (21 pages), available commercial low-sodium products and sodium content of water-packed fruits. There is a good index; the printing is excellent, with a large type on light, nonglare paper. The book should be in all medical libraries and available to dietitians and physicians.

Modern Concepts of Leprosy. By Harry L. Arnold, Jr., M.D., Member, Department of Dermatology, Straub Clinic, Honolulu, Hawaii, and contributing editor, *International Journal of Leprosy.* 8°, paper, 105 pp., with 33 illustrations and 6 tables. Springfield, Illinois: Charles C Thomas, 1953. $3.75. (Publication No. 145, *American Lecture Series.*)

Dr. Arnold has written this monograph to provide a short account of leprosy, especially for dermatologists. It presents more material than is found in the ordinary textbook, and discusses in order the etiology, epidemiology, classification, diagnosis, the lepromatous and tuberculoid forms, treatment and prevention. Lists of references are appended to the chapters, and there is a general bibliography of 105 items. There is a good index, and the publishing, especially the illustrations, is excellent.

Contact Dermatitis. By George L. Waldbott, M.D., senior physician, Harper Hospital, chief, Division of Allergy and assistant physician, Grace Hospital, and chief, Allergy Clinic, Children's Hospital of Michigan. 8°, cloth, 218 pp., with 131 illustrations and 16 tables. Springfield, Illinois: Charles C Thomas, 1953. $8.75. (Publication No. 133, *American Lecture Series.*)

This comprehensive monograph is based on thirty years' experience in the practice of allergy. The author believes that contact dermatitis is the most common skin disease; he discusses the mechanism, pathology, diagnosis, determination of the causes and the pattern, including the body surface and the hands, 54 pages being devoted to the hands alone. There are chapters on "special situations," discussing poison ivy, pollen dermatitis, cosmetics, soaps, wearing apparel, footwear, drugs, occupational dermatitis and pruritus ani and vulvae, and treatment. The appendixes list the principal contact agents and other irritants for various occupations, and provide a glossary of terms. There is a bibliography of 210 items and a good index. The 16 tables throughout the text furnish valuable information in condensed form. The sections on patters are profusely illustrated, and the publishing is excellent. The monograph should be in all medical libraries and available to all persons interested in this type of dermatitis.

Fibrocystic Disease of the Pancreas: A congenital disorder of mucus production—mucosis. Edited by Martin Bodian, M.D., director, Department of Morbid Anatomy, Hospital for Sick Children, London. 8°, cloth, 244 pp., with 121 illustrations. New York: Grune and Stratton, 1953. $9.50.

This monograph is the joint work of three physicians, Martin Bodian, A. P. Norman, and C. O. Carter. The text is divided into six main parts on history of the condition, clinical material, familial incidence, pathology, case summaries (116 in number) and pancreatic dysplasias. There is a list of references and an index. The printing was done in England and is excellent.

Shoulder Lesions. By H. F. Moseley, M.A., D.M., M.Ch. (Oxon.), F.R.C.S. (England and Canada), Hunterian professor, Royal College of Surgeons of England, assistant professor of surgery, McGill University Faculty of Medicine, and associate surgeon, Royal Victoria Hospital, Montreal. Second edition. 4°, cloth, 329 pp., with 43 medical illustrations in full color by Helen MacArthur, B. A. New York; Paul B. Hoeber, Incorporated, 1953. $12.00.

This semi-atlas was first published in 1947. Two chapters on fractures in the shoulder region, and on the clavicular regions have been added. A preliminary report has been made on the treatment of articular disorders with cortisone and ACTH. The text has been revised, and there is a good index. The chapter on the neurologic aspects of shoulder pain is by F. L. MacNaughton, and that on x-ray diagnosis and treatment by C. P. Peirce and Jean Bouchard. The publishing is excellent. The book should be in all collections on orthopedics.

Handbook of Treatment of Acute Poisoning. By E. H. Bensley, M.B.E., M.D., director, Department of Metabolism and Toxicology, Montreal General Hospital, and associate professor of experimental medicine and lecturer in toxicology, McGill University Faculty of Medicine; and G. E. Joron, M.D., C.M., Dip. Int. Med., junior assistant, Department of Medicine and Department of Metabolism and Toxicology, Montreal General

Hospital, demonstrator in medicine, McGill University Faculty of Medicine, and clinical assistant, Department of Medicine, St. Mary's Hospital, Montreal. 16°, cloth, 201 pp. Montreal: Renouf Publishing Company, Limited, 1953. $2.50.

In this small handbook the authors present information on the basic principles, general plan and methods of treatment, and the common types of acute poisoning.

Dermatology in General Practice. By Jacob H. Swartz, M.D., assistant professor of dermatology, Harvard Medical School, and consulting dermatologist, Massachusetts General Hospital. With a foreword by C. Guy Lane, M.D., consulting dermatologist, Massachusetts General Hospital. 8°, cloth, 581 pp., with 252 illustrations. Baltimore: Williams and Wilkins, 1953. $11.00.

This new book on diseases of the skin is written primarily for the general practitioner, student and nurse. Special emphasis is placed on the clinical picture, differential diagnosis and treatment of the more common skin diseases. A discussion of the relation of the dermatoses to systemic diseases is given when applicable. Dr. Swartz, who is a recognized authority on the mycoses, has written a chapter of 78 pages on the mycotic infections. Lists of references are appended to the chapters. There is a good index, and the book is well published.

NOTICES

HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, November 17, at 8:15 p.m. The following program will be presented by the Department of Biochemistry, Harvard Medical School, and Professor A. Baird Hastings will preside:

Potentiometric Studies on the Diphosphopyridine Nucleotide System. Dr. F. L. Rodkey.

The Measurement of Total Glucose Phosphorylation in Normal and Diabetic Liver Slices. Drs. A. Renold and A. B. Hastings and Miss Frances Nesbett.

Some Observations of the Action of Estradiol in Vitro. Drs. C. A. Villee and D. D. Hagerman.

Enzymes Involved in the Metabolic Error of Alkaptonuria. Drs. S. W. Edwards and W. E. Knox.

NEW ENGLAND CONFERENCE ON ALLERGY AND RELATED SUBJECTS

The sixth meeting of the New England Conference on Allergy and Related Subjects will be held on December 2. The afternoon program (presentation of cases) will be held in Stearns Auditorium, New England Center Hospital, Boston, from 3 to 5 p.m. The evening program will be held at the Harvard Club, Boston, at 8:30 p.m. Dr. Robert A. Cooke, director, Department of Allergy, Roosevelt Hospital, New York City, will speak on the subject "Bacterial Allergy."

Reservations for the dinner, which will be served at the Harvard Club at 7:15 p.m., must be made by November 27 with Dr. Irving W. Schiller, 65 East Newton Street, Boston 18, and a check for $5.50 should be enclosed.

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE AIDS FOR THE BLIND

A symposium on Communication Aids for the Blind will be held in conjunction with the one hundred and twentieth meeting of the American Association for the Advancement of Science, in Room E, Mechanics Building, Huntington Avenue, Boston, on Monday, December 28, at 9:30 a.m. This symposium will feature demonstrations of experimental developments in travel aids for the blind, and will present current trends in research.

PHI DELTA EPSILON FRATERNITY DANCE

A cocktail party and dance for graduates and undergraduates of the Phi Delta Epsilon fraternity will be held at the Hotel Beaconsfield, Brookline, on Saturday, November 28 at 8:00 p.m. All members in the New England area are invited.

POSITION IN QUARTERMASTER RESEARCH CENTER

A position is available for a physician to take charge of a dispensary in a large new federal research organization in Natick, Massachusetts. The salary is $7000 a year for a forty-hour week. Information may be obtained from the Personnel Officer, Quartermaster Research Center, Natick, Massachusetts.

NEW YORK AND BROOKLYN REGIONAL COMMITTEE ON TRAUMA, AMERICAN COLLEGE OF SURGEONS

A course in surgery of the hand will be presented by the New York and Brooklyn Regional Committee on Trauma of the American College of Surgeons at the Einhorn Auditorium, Lenox Hill Hospital, New York City, on December 11 and 12.

Further information may be obtained from Dr. Frederick M. Smith, Secretary, 180 Fort Washington Avenue, New York 32, New York.

INTERNATIONAL COLLEGE OF SURGEONS, REGIONAL MEETING

A regional meeting of the United States Section, International College of Surgeons, including the states of California, Nevada, Oregon, Arizona and Washington, will be held at the Ambassador Hotel in Los Angeles, November 28 and 29. The meeting is open to all members of the medical profession.

Other regional meetings of the United States Section of the International College of Surgeons will be scheduled as follows: January 22 and 23, Oklahoma City; January 29 and 30, West Palm Beach; and July 22 and 23, Salt Lake City.

The ninth International Congress of Surgery will be held in Sao Paulo, Brazil, April 26 to May 2, 1954.

The nineteenth Annual Congress of the United States and Canadian Sections of the College will be held at the Palmer House, Chicago, September 7 to 10, 1954.

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 16 and 17. New England Diabetes Fair. Horticultural Hall. Page 750, issue of October 29.

NOVEMBER 16–DECEMBER 21. Hartford Medical Society Program. Page 260, issue of August 6.

NOVEMBER 17. Harvard Medical Society. Notice above.

NOVEMBER 17 and 19. Warren Prize Lectures. Page 750, issue of October 29.

NOVEMBER 17–DECEMBER 15. Boston City Hospital House Officers' Association Lectures. Page 789, issue of November 5.

NOVEMBER 18. Massachusetts Society of Examining Physicians. Page 546, issue of September 24.

NOVEMBER 18. Middlesex South District Medical Society. Page 790, issue of November 5.

NOVEMBER 18 and 25. Consultation Clinics for Crippled Children. Page 713, issue of October 22.

NOVEMBER 18–DECEMBER 2. Course in Child Psychiatry (Pediatric Neuropsychiatry). Page 428, issue of September 3.

NOVEMBER 19 and 20. Inter-Society Cytology Council. Page 170, issue of July 23.

NOVEMBER 20–DECEMBER 18. Boston Lying-in Hospital Journal Club. Page 672, issue of October 15.

NOVEMBER 23. Symposium on Nursing. Page 714, issue of October 22.

NOVEMBER 28. Phi Delta Epsilon Fraternity Dance. Notice above.

NOVEMBER 28 and 29. International College of Surgeons, Regional Meeting. Notice above.

DECEMBER 2. New England Conference on Allergy and Related Subjects. Notice above.

DECEMBER 6. American Academy of Dental Medicine. Page 170, issue of July 23.

DECEMBER 11 and 12. New York and Brooklyn Regional Committee on Trauma, American College of Surgeons. Notice above.

DECEMBER 28. American Association for the Advancement of Science. Notice above.

JANUARY 6, MARCH 3 and APRIL 21, 1954. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

FEBRUARY 2–4. Examination for Public Health Service Medical Officers. Page 750, issue of October 29.

FEBRUARY 15–20. Pan-American Academy of General Practice. Page 790, issue of November 5.

MAY 31–JUNE 3. American Urological Association. Page xvii, issue of July 23.

SEPTEMBER 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

MIDDLESEX EAST

NOVEMBER 18.
JANUARY 20. (Combined with the Auxiliary.)
MARCH 24.
MAY 11. Annual Meeting. (Harlow Dinner.)

(*Notices concluded on page xxi*)